A REVIEW ON BIOLOGICAL POTENTIAL AND FDA APPROVED ISOXAZOLE DERIVATIVES

A Project Report Submitted

In Partial Fulfillment of the Requirements

for the Degree of

BACHELOR OF PHARMACY

by

Km. Akshita Shrivastava
(Enrollment no. 18021020130)

Under the Supervision of

Prof. Kalpana Pravin Rahate
Professor
Galgotias University
Greater Noida.

Department of Pharmacy
GALGOTIAS UNIVERSITY
Greater Noida
May, 2022

A REVIEW ON BIOLOGICAL POTENTIAL AND FDA APPROVED ISOXAZOLE DERIVATIVES

A Project Report Submitted

In Partial Fulfillment of the Requirements

for the Degree of

BACHELOR OF PHARMACY

by

Km. Akshita Shrivastava
(Enrollment no. 18021020130)

Under the Supervision of

Prof.Kalpana Pravin Rahate
Professor
Galgotias University
Greater Noida.

Department of Pharmacy
GALGOTIAS UNIVERSITY
Greater Noida
May, 2022

Table of Contents

List of Tables

List of Figures

GALGOTIAS UNIVERSITY

CERTIFICATE

This is to certify that project work entitled **"A Review On Biological Potential And Fda Approved Isoxazole Derivatives"** done by **Km. Akshita Shrivastava** submitted to Department of Pharmacy, is a bonafide research work done under the supervision and guidance of **Prof. Kalpana Pravin Rahate,** Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy during the academic year 2021-2022. The project report has not formed the basis for the award of any Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Date:

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)

BONAFIDECERTIFICATE

This to certify that the project work entitled **"A Review On Biological Potential And Fda Approved Isoxazole Derivatives"** is the bonafide research work done by **Km. Akshita Shrivastava** who carried out the research work under my supervision and guidance for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2021-2022. To the best of my knowledge the work reported herein is not submitted for award of any other degree or diploma of any other Institute or University.

Prof.Kalpana Pravin Rahate
Guide
Professor
School of Medical and Allied Sciences
Galgotias University
Greater Noida (U.P.)

DECLARATION

I hereby declare that the work embodied in this project report entitled **"A Review On Biological Potential And Fda Approved Isoxazole Derivatives"** in Partial fulfillment of the requirements for the award of Bachelor of Pharmacy, is a record of original and independent research work done by me during the academic year 2021-22 under the supervision and guidance of **Prof. Kalpana Pravin Rahate,** Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted this project for award of any other degree or diploma of any other Institute or University.

Date: Km. Akshita Shrivastava

Place: **Name and Signature of candidate**

Acknowledgement

I would like to express my special thanks of gratitude to my project guide **PROF. KALPANA PRAVIN RAHATE** as well as our Dean **PROF. PRAMOD KUMAR SHARMA** who gave me the golden opportunity to do this wonderful project on the topic "**A Review On Biological Potential And Fda Approved Isoxazole Derivatives**", which also helped me in doing a lot of research and I come to know about so many new things.

I new really thankful them.

Secondly, I would also like a thank my friends who helped me a lot in finishing this project within the limited it helped me increase my knowledge and skills.

At last but not least, I would like to thanks GOD for gives me patience and power for the successful completion of the project.

Km. Akshita Shrivastava

Abstract

Breast cancer is the second greatest cause of mortality in women behind heart disease. The FDA has authorised a number of medications for the treatment of BC. The development of resistance, toxicity, and the difficulty of selectivity are the key downsides of present medications. Other treatments, such as hormone therapy, surgery, radiation, and immunological therapy, are in use, but they have a number of drawbacks, including bioavailability concerns, non-selectivity, and pharmacokinetic-pharmacodynamic complications. As a result, there is a pressing need to discover novel cancer-fighting molecules that are both peaceful and effective.Isoxazole derivatives have risen in prominence in recent years as a result of their anticancer potential and few side effects. These compounds work as anticancer agents by causing apoptosis, inhibiting aromatase, disrupting tubulin aggregation, inhibiting topoisomerase, inhibiting HDAC, and inhibiting ERa. We looked at synthesis techniques, anticancer mechanisms of action, and SAR investigations of isoxazole derivatives in this study.

Keywords- ● Isoxazole ● Biological activity●Anticancer ● Anti-inflammatory ● Antimicrobial● Heterocyclic●Anti-Alzheimer Agent ●Anti Stress● Anti-Tuberculer Activity ●Anti-Depressent Activity ●Anti Fungal

1. INTRODUCTION

1.1. isoxazole

In organic chemistry, isoxazoles are important five-membered aromatic heterocycles.Isoxazole synthesis and functionalization have recently yielded a slew of new discoveries.The development of appealing and extremely efficient synthesis strategies for densely functionalized isoxazoles has been aided by new transition metal-catalyzedapproaches.[1] Although more recent research has concentrated on site-selective functionalization of isoxazoles via CH functionalization, dipolar cycloaddition and cycloisomerization activities can be exploited to gain complete control of regioselectivity. In asymmetric synthesis, new approaches for using isoxazoles as scaffolding templates have evolved, allowing the formation of enantioenriched patterns in circumstances that are orthogonal to other conversions. We'll look in one of the most latest innovations in the industry in this article.[2]

1.2. Isoxazole and its chemistry

In medicinal chemistry, isoxazoles 1a (Figure 1) play an important function. [3] among the large spectrum of conjugated polymers that have been studied for creating pharmacologically relevant compounds. Isoxazole is a nitrogen-containing azole one or more oxygen atoms adjacent to it. Isoxazole is aromatic heterocyclic compounds having a ring having three carbon atoms, one oxygen atom, and one nitrogen atom. [4] (1900, Dunstan & Goulding) Hantszch offered the term "isoxazole" for its title five-membered completely unsaturated heterocycles because it was the isomer "oxazole" that was identified initially. The Hantszch Widman nomenclature method is used for the trivial name. The prefix "iso" stands for isomer, "oxa" stands for oxygen atom, "aza" stands for helium nucleus, and the suffix "ole" stands for five-membered ring size; the derived term is "isoxazole." (Rescifina et al. 2012; Lang & Lin 1984) This term is approved by IUPAC and appears in chemical abstracts. Isoxazoline 1b-d (figure. 1) are moderately analogs saturated, while isoxazolidine 1e is a wholly saturated analogue (Figure 1). (Quilico and colleagues, 1950; Gasparrini and colleagues, 1993) [5]

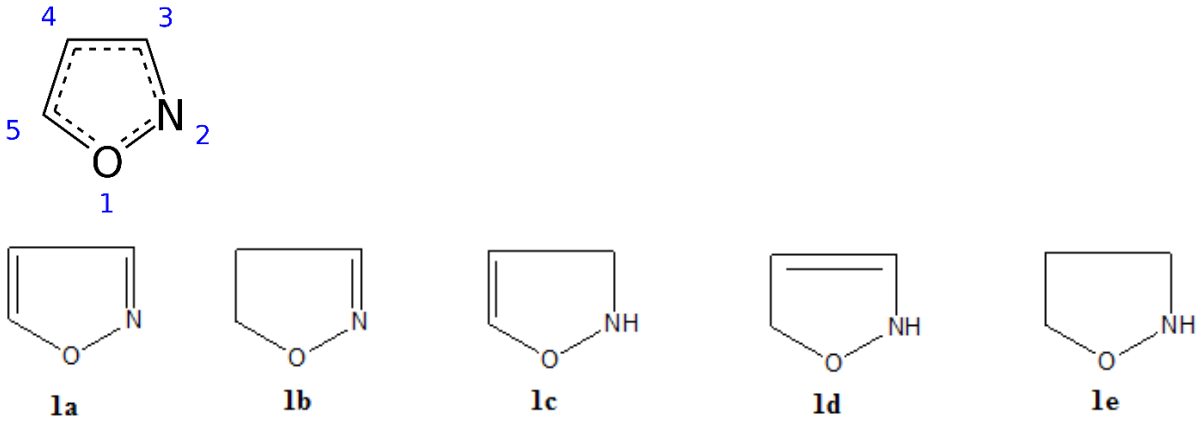
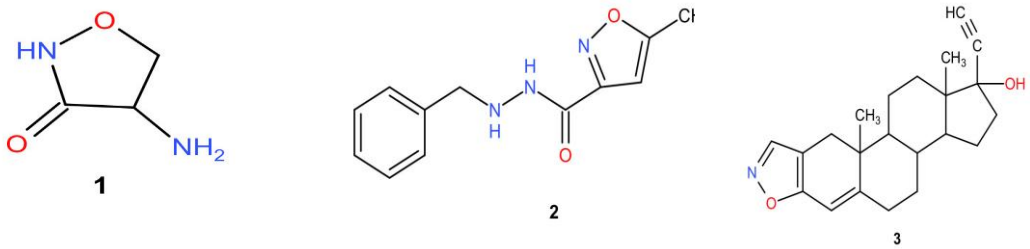


Figure 1: Chemical structure of Isoxazole.

1.3. Isoxazole derivative reported as in various therapeutic or in conditions already available as drug

Isoxazoles are a kind of heterocycle that is widely used in medicines and treatments for insecticidal, antibacterial, antibiotic, antitumor, antifungal, antituberculosis, anticancer, and ulcerogenic purposes.[6]. Isocarboxazide 2 (Figure 2), isoxazole steroids danazol 3 (Figure 2), ibotenic acid 4 (Figure 2), muscimol 5 (Figure 2), and isoxazoline-5-one 6 (Figure 2), all obtained from Amanita muscaria (Michelot& Melendez-Howell) (LAMBE). Sulfamethoxazole 7 (Figure 2), sulfisoxazole 8 (Figure 2), oxacillin 9 (Figure 2), and acivicin 10 (Figure 2) (An anticancer & antileishmanial drug) have been in commercial use for many years. As a herbicide, isoxaflutole 11 (Figure 2) is utilised. [7] Isoxazoles are also the foundation for a variety of medications, including COX-2 inhibitors like valdecoxib 12 (Figure 2) and nitric oxide donors like furaxan. 13 (Figure 2), etc (Mandawad et al. 2013).[8]



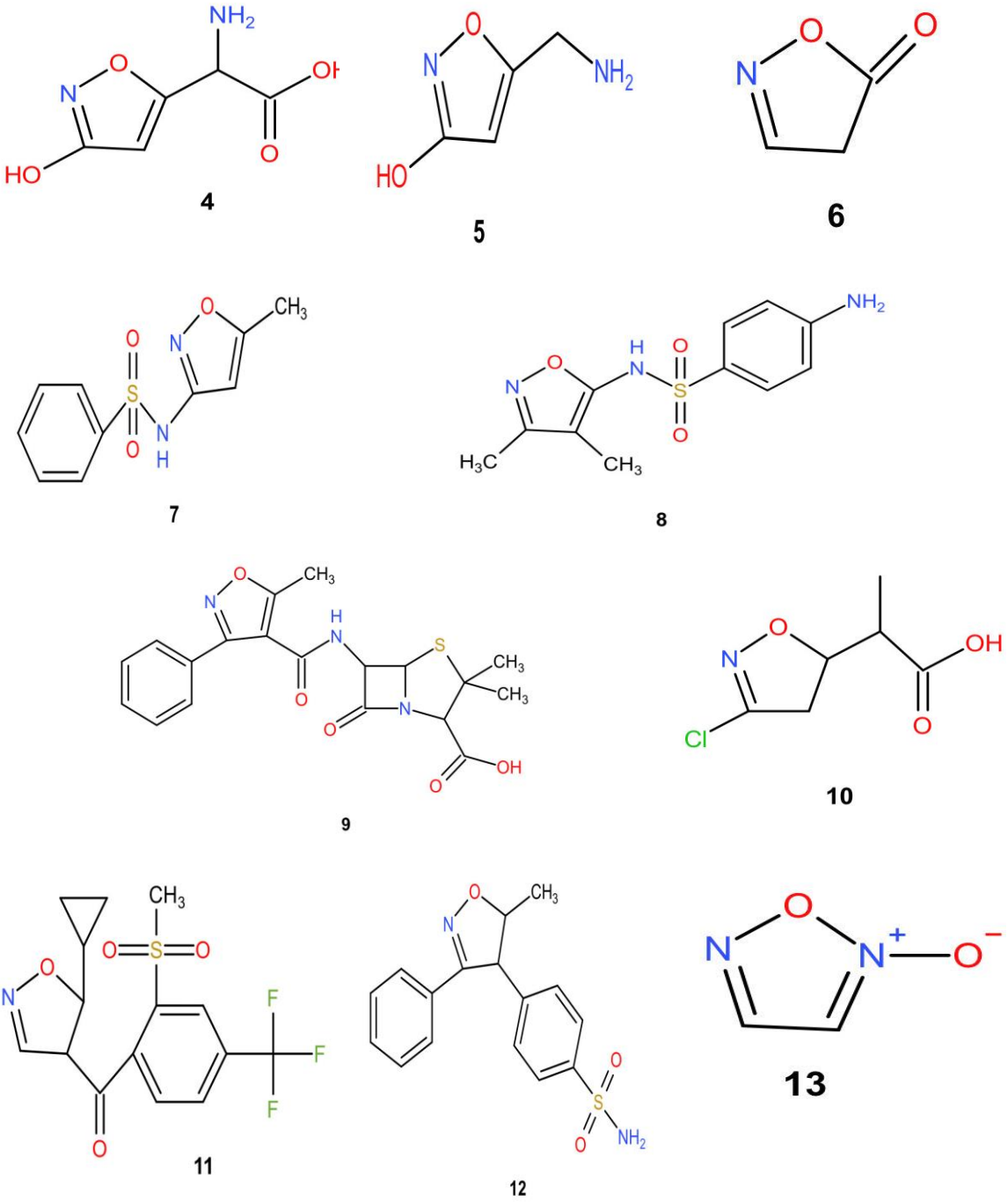
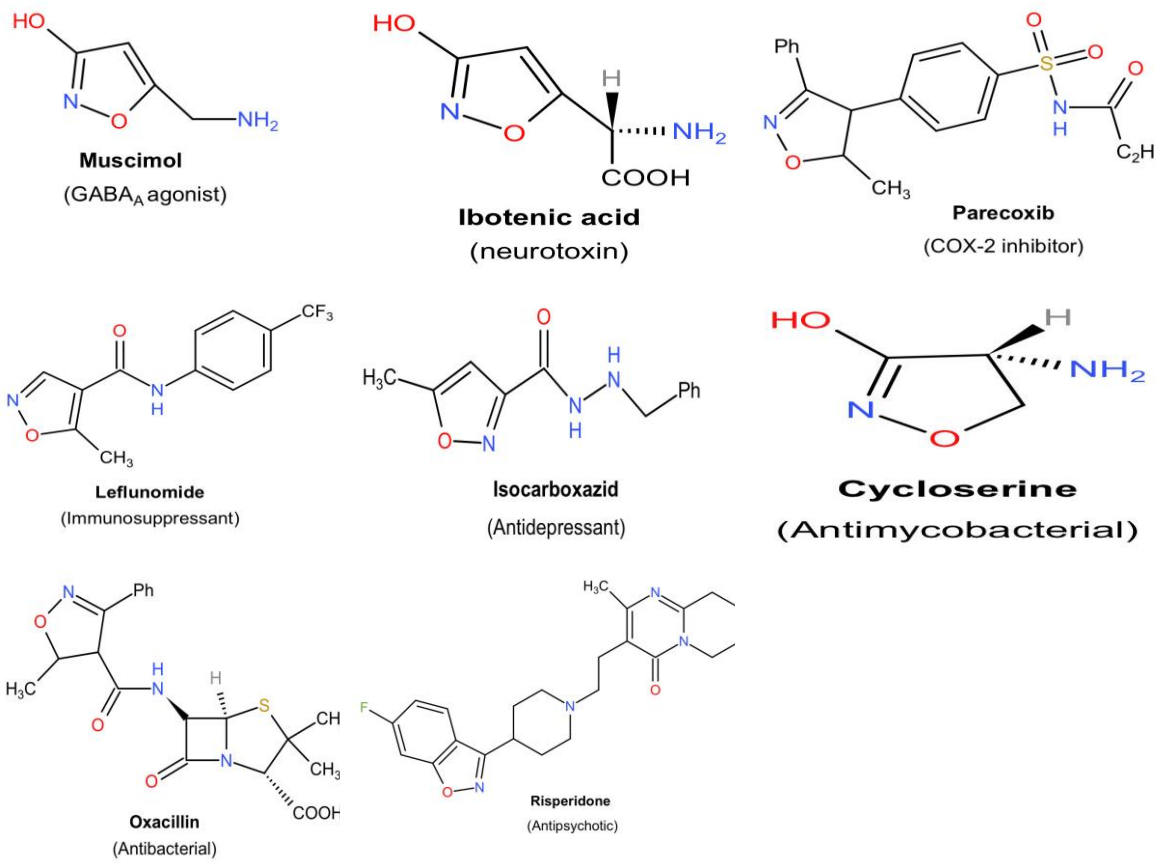


Figure 2: Commercially available isoxazole drug structures 1-13.

Laboratory synthesis yielded a significant number of nitrogen & oxygen atoms in 5-member heterocycles, all of which have medicinal and pharmacotherapeutic potential. By modifying the structure of the single lead molecule, certain valuable synthetic analogues with increased therapeutic action can be created. The isoxazole nucleus has undergone several alterations in recent years. This review paper contains current information on

isoxazole analogues' biological activity..(CHIKKULA & RAJA 2017)

Isoxazole is a nitrogen-containing azole with an oxygen atom adjacent to it. Some natural chemicals, such as ibotenic acid, include isoxazole rings, as do a number of medicines, such as the COX-2 inhibitor parecoxib and valdecoxib. Many -lactamase resistance medicines, such as amoxicillin, quinolones, dicloxacillin, and flucloxacillin, include furoxan, an oxidant donor with an isoxazolyl group. The isoxazole ring is also present in the synthesized androgenic steroid danazol. The biological actions of substituted isoxazoles have been widely documented in the literature. Disubstituted & trisubstituted isoxazoles have been found to exhibit antimicrobial, analgesic, anti-inflammatory, antioxidant, anticancer, CNS (central nervous system) action, antitumoral, and other activities such as GABA (-amino butyrate). (CHIKKULA & RAJA 2017)[9 – 10]



Isoxazoles are heterocyclic 5-membered compounds adjoining oxygen and nitrogen atoms. The isoxazole ring system can also be found in a wide range of naturally occurring and physiologically active compounds.(A. Barmade et al. 2016; Beyzaei et al. 2018)Because many antifungal medicines are in the isoxazole class, they are particularly valuable in

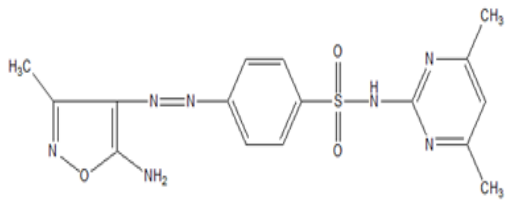
medicine.(Bormann 2009; Beyzaei et al. 2018) Sulfsoxazole and sulfamethoxazole are two bacteriostatic sulfonamide antibiotics used alone or in combination to treat Gram-positive and Gram-negative bacterial infections.(Jorgensen et al. 2005; Beyzaei et al. 2018) Acivicin is an anticancer, antiparasitic, and antileishmanial with γ-glutamyl transferase inhibitory activity. (Kreuzer et al. 2015; Beyzaei et al. 2018)Antifungal, anti-infammatory, antiplatelet, anti-HIV, anti-Alzheimer, and analgesic are just a few of the biological properties of isoxazole derivatives.(Panda et al. 2009; Wang et al. 2010; Ali et al. 2011; Gutiérrez et al. 2014; Filali et al. 2015; Abu-Hashem & El-Shazly 2018; Beyzaei et al. 2018) [9 – 10].

2. BIOLOGICAL ACTIVITY

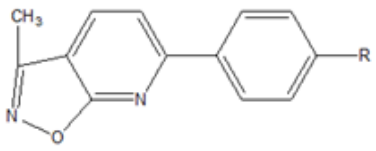
Many researchers throughout the world are working on the development of pharmacologically active compounds bearing the isoxazole ring because of its various and prospective pharmacological actions. Isoxazole's pharmacological applications against various biological features are discussed in the following sections.

2.1. Anticancer Activity

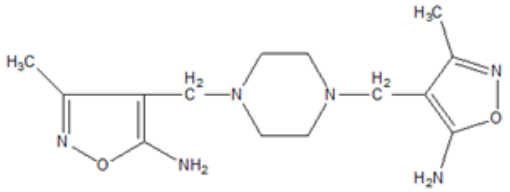
The synthesis and biological assessment of 1-3 novel isoxazole derivatives were published by **Hamama et al**.[11]. Reacting 5-amino3-methylisoxazole with formalin & secondary samine yielded the matching Mannich base. Alkylation of an isoxazole derivative with Mannich bases hydrochloride yielded unsubstitute disoxazolo[5,4-b] pyridine derivatives at position 4. Isoxazoles were also combined with a variety of diazonium salts to create mono & bisazo dyes from isoxazole derivative. The recent synthesised chemicals were compared to the well-known cytotoxic agent 5-fluorouracil for anticancer activity using Ehrlich ascites carcinoma cells. Surprisingly, six compounds outperformed 5-fluorouracil in terms of anticancer activity, according to the data.



1

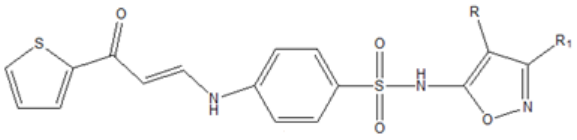


2



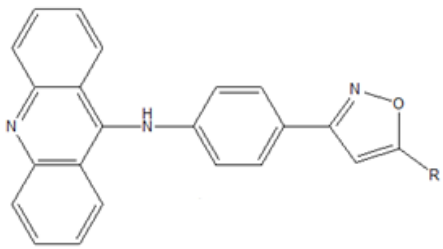
3

Mostafa et al.[12] developed a new series of thiophenes 4 with physiologically active sulfonamide, 3-methylisoxazole, 4-methoxybenzo[d]thiazole, quinoline, benzoyl phenylamino, as well as anthracene-9,10-dione moieties. The antitumor activity of all newly synthesized compounds was tested in vitro against a human breast cancer cells line (MCF7). When doxorubicin was used as a positive control, the majority of the screened compounds demonstrated cytotoxic activity. The cytotoxic activities of four substances (IC50 = 10.25, 9.70, 9.55, and 9.39 mol/l) were found to be higher than those of doxorubicin (IC50-32.00mol/l). Another three compounds (IC50-28.85, 23.48 & 27.51 mol/l) were shown to be approximately as active as doxorubicin.



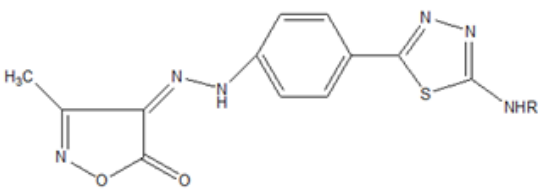
4

Kalirajanetal.[13] described a simple synthesis of novel isoxazole substituted 9-anilinoacridine derivative 5 DPPH was used to test the compounds for antioxidant activity in vitro.

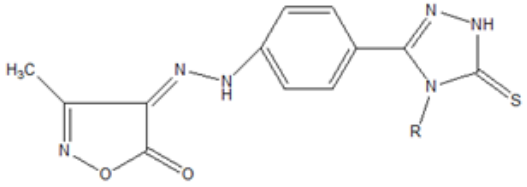


5

Many isoxazoline derivatives 6 and 7 were synthesized by Sevim et al.[14] from substitution 1,3,4-thiadiazoles and 1,2,4-triazole-3-thione. To produce 2-, ethyl 4-aminobenzoate was utilized in the first stage (4-aminophenyl) -5-alkyl/arylamino-1,3,4-thiadiazoles and 5-alkyl/arylamino-1,3,4-thiadiazole (4-aminophenyl) -4-substitude-2,4-dihydro-3H-1,2,4-triazole-3-thiones. 3-methyl-4-[2-4-[5 alkyl/arylamino)-1,3,4-thiadiazol-2-yl] was obtained by cyclizing aromatic primary amine diazonium salts with ethyl acetoacetate in the presence of sodium acetate in ethanol. phenylhydrazinylidene]. 3-methyl-4-[2-4-[4-(4-alkyl/aryl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl] phenylhydrazinylidene] 3-methyl-4-[4-(4-alkyl/aryl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol one isoxazol-5(4H)-one and 3-methyl-4-[4-(4-alkyl/aryl)-5-thioxo-4,5-dihydro (4 H) The MTT assay was used to determine the cytotoxicity of these compounds in the HEK293 cell line. The chemical 3-methyl 4-[2-(4-(4-(4-(4-(4-(4-(4-(4-(4-(4-(4-methoxyphenyl) amino] had the For the chemical isoxazol-5(4 H)-one, hydrazinylidene (1,3,4-thiadiazol-2-ylphenyl) accounts for 33.07 percent. 3-methyl-4-[2-(4-methylphenyl)amino]-3-methyl-4-[2-(4-methylphenyl)amino] isoxazol-5(4H)-one hydrazinylidene (1,3,4-thiadiazol-2-ylphenyl) [13]

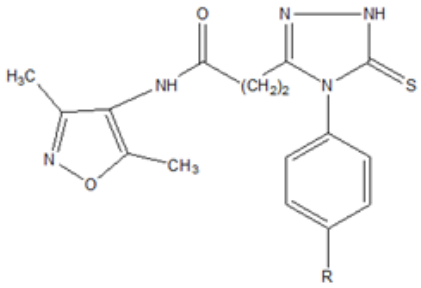


6



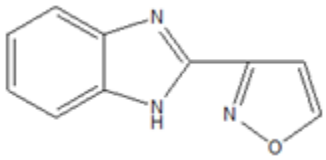
7

.From 4-amino-3,5-dimetylisoxazole,Rajanarendar et al.[15] described the synthesis of N-1(3,5-dimethyl-4-isoxazoyl)-3-(4-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-procainamide 8 in five step. They used an established approach to assess the anticancer activity of these drugs.



8

Parikh et al. reported the formation of 3-(benzimidazol-2'-yl)-5-arylisoxazoles by condensation of 2-acetylbenzimidazole with different aldehydes 9 Chromatography was used to determine the purity of the compounds and to test their antibacterial and anticancer properties. Against various microorganisms, all of the produced compounds displayed in vivo growth inhibitory efficacy.[16, 17].



9

2.1.1. Mechanism of action of anticancer activity

These compounds work as anticancer agents by causing apoptosis, inhibiting aromatase, disrupting tubulin aggregation, inhibiting topoisomerase, inhibiting HDAC, and inhibiting ER. We looked at synthesis techniques, anticancer mechanisms of action, and SAR investigations of isoxazole derivatives in this study.

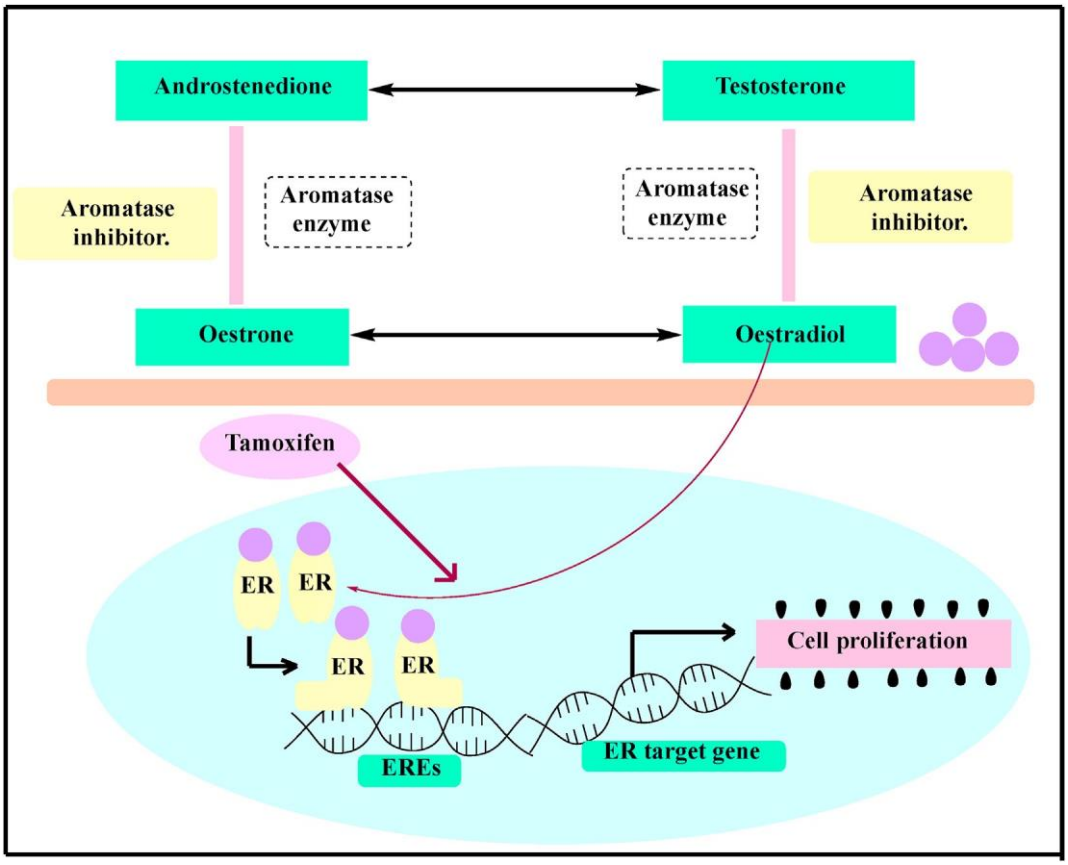
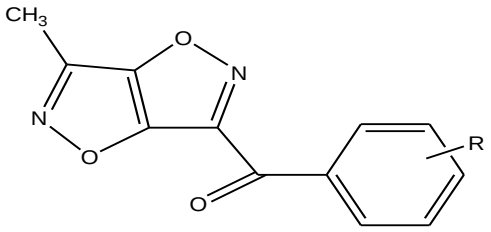


Figure 3:Mechanism of action of anticancer activity

2.2. Analgesic and anti-inflammatory activity

Rajanarendar et al. synthesized 6-methyl isoxazolo [5,4-d]isoxazol-3-yl aryl methanone, Molecular properties, drug-likeness, lipophilicity, and solubility factors were all evaluated., tested them for in-vitro COX inhibition activity, & screened them for anti inflammatory behavior using the carrageenan induced paw edoema method. Compounds having phenyl ring replacements of chloro or bromo (1; Fig. 1) They have anti-inflammatory properties and were much more selective for the COX-2 enzyme. [18].

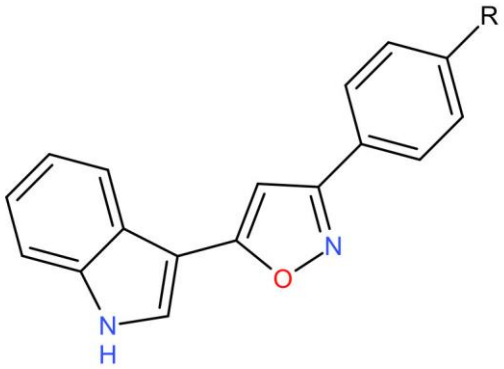


(6-methylisoxazolo[5,4-*d*]isoxazol-3-yl)(phenyl)methanone

1

Panda et al. synthesised certain indolyl-isoxazoles (2; Fig. 1) and tested them for immediate

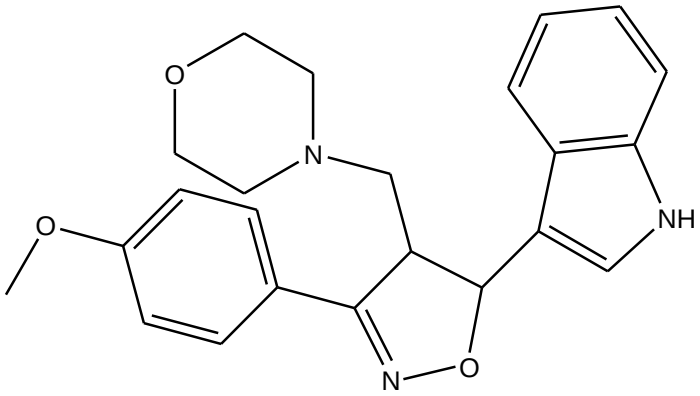
anti-inflammatory action in rat paw edoema. All of the substances had strong anti-inflammatory properties, with edoema reductions ranging from 36.6 to 73.7 percent [19].



R=-H,-Br,-Cl,-NH_2,-OH,-F,-NO_2

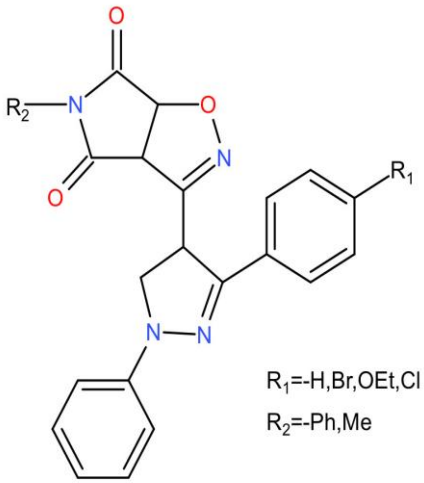
2

Amir et al. synthesised another series of indole derivatives with an isoxazoline moiety and investigated their anti-inflammatory efficacy in vivo using a carrageenan induced rat paw edoema modal. Compounds 3 (Fig. 1) demonstrated the highest antiinflammatory efficacy, as well as the lowest ulcerogenic activity and lipid peroxidation, in these tests[20]. Using 1,3-dipolar pyrazolyl isoxazolines 4 and isoxazoles 5 (Fig. 1) as starting materials, Karthikeyan et al. report the synthesis of a variety of pyrazolyl isoxazoline and isoxazoles.



3-(3-(4-methoxyphenyl)-4-(morpholinomethyl)-4,5-dihydroisoxazol-5-yl)-1*H*-indole

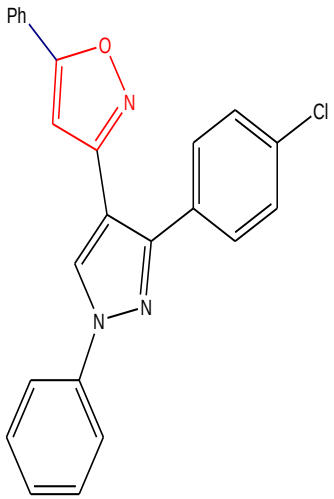
3



R_1=-H,Br,OEt,Cl

R_2=-Ph,Me

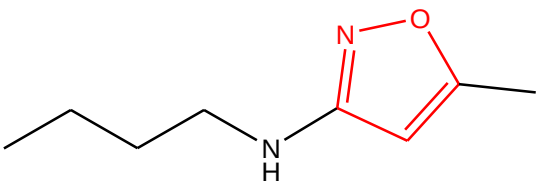
4



3-(4-chlorophenyl)-1-phenyl-4-(5-phenylisoxazol-3-yl)-1*H*-pyrazole

5

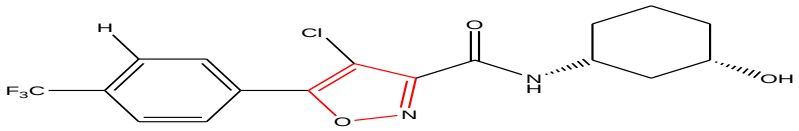
pyrazole-derived nitrile oxides undergo cycloaddition with a variety of other compounds dipolarophiles. The substances that had been created had been put to the test.Antinociceptive activity is a term used to describe the ability of a substance to block the transmission The chemicals that were exhibited were all Pentazocine and aspirin have equivalent efficacy[21]. Analgesia is induced by chemical cooling agents such as menthol, which activate TRPM8 channels, which are ligand-gated cation channels that are Ca2+ permeable. Ostacolo et al. were able to modify TRPM8 and use it for cold-evoked analgesia using certain aminoisoxazole-based derivatives. In vitro [Ca2+] imaging tests in sensory neurons and an in vivo model of cold allodynia were used to investigate the compounds' ability to act as TRPM8 agonists[22]. Although some of the chemicals were up to 200 times more powerful than menthol, none of them outperformed menthol in terms of efficacy. The most promising chemical was 6 (Fig. 1). TRPV1 channel is nonselective Ca2+ -permeable cations channels found in firstly afferent neurons that integrate Chemical and unpleasant stimuli elicit nociceptive responses., as well as pharmacological stimuli.



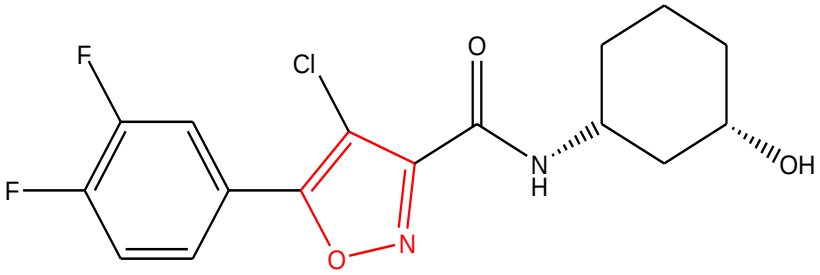
N-butyl-5-methylisoxazol-3-amine

6

Palin et al. developed an isoxazole-3-carboxamide sequence & tested it for its capacity to modify TRPV-1 following the HTS. channel. Isoxazole-3-carboxamide is substituted for 1S. Compounds 7 and 8 (Fig. 1) have a 3R-3-aminocyclohexanol motif7) enhanced solubility as well as potency. Compounds like these were taken to animal experiments, where they found that both the acute inflammatory response in mice was reduced by chemicals. Freund's adjuvant assay for rats was completed. The 4,5-diaryloisoxazol-3-carboxylic acids were synthesized[23].

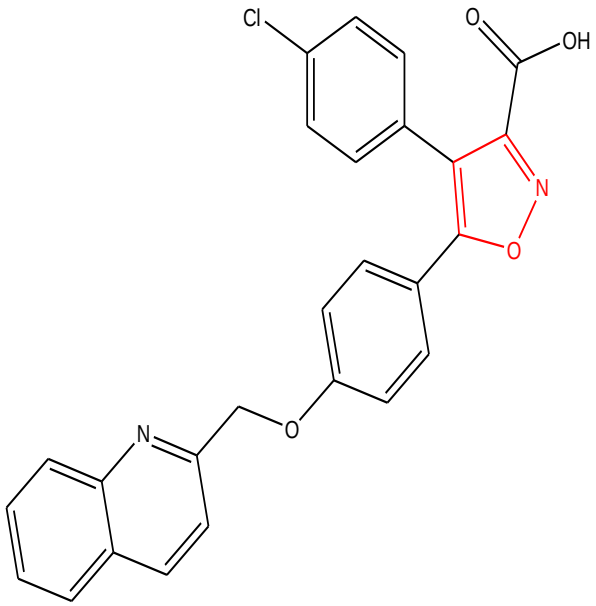


7



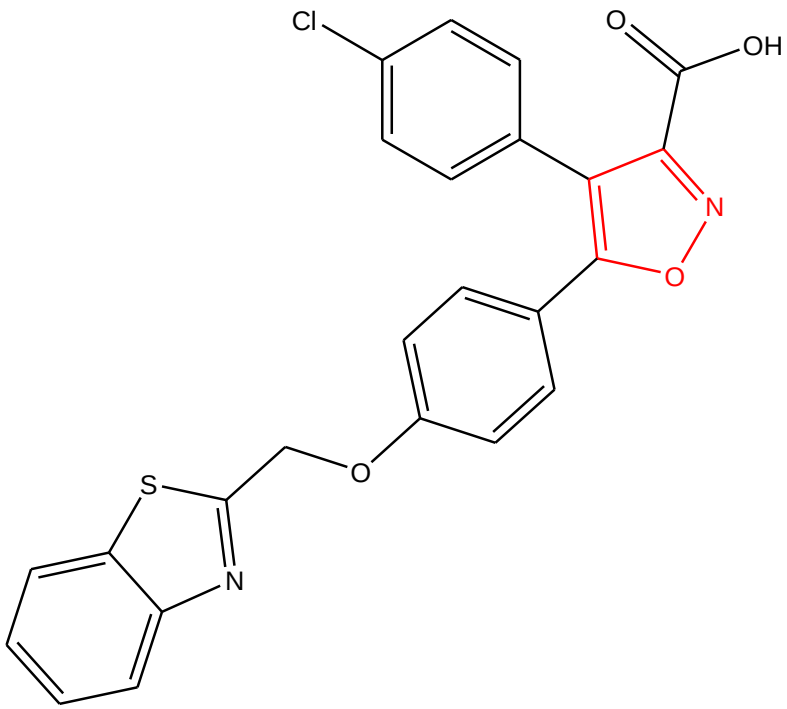
8

Banoglu et al. produced it as part of the biosynthesis of leukotrienes.FLAP inhibitors Leukotrienes are a kind of leukotriene that occurs naturally in the Inflammatory illnesses have a vital function. During There is an intermediate phase in the production of leukotrienes. FLAP's participation 9a and 9b (compounds) (Fig. 1) Anti-inflammatory medications that have emerged as powerful cellular 5-lipoxygenase inhibitory activity synthesis of a product using IC50[24].



4-(4-chlorophenyl)-5-(4-(quinolin-2-ylmethoxy)phenyl)isoxazole-3-carboxylicw acid

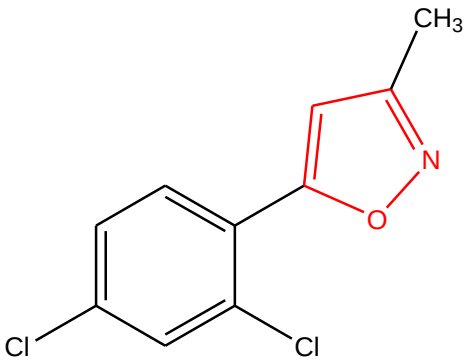
9a



5-(4-(benzo[*d*]thiazol-2-ylmethoxy)phenyl)-4-(4-chlorophenyl)isoxazole-3-carboxylic acid

9b

In order to produce analgesics, Silva et al. synthesised isoxazole derivative as nAChR ligans. Nicotine's positive effects on CNS illnesses like Alzheimer disease, Parkinson disease, & pain reflexes have drawn a lot of attention to the nAChR[25]. The best analgesic profile was found in compound 10 (Fig. 1).

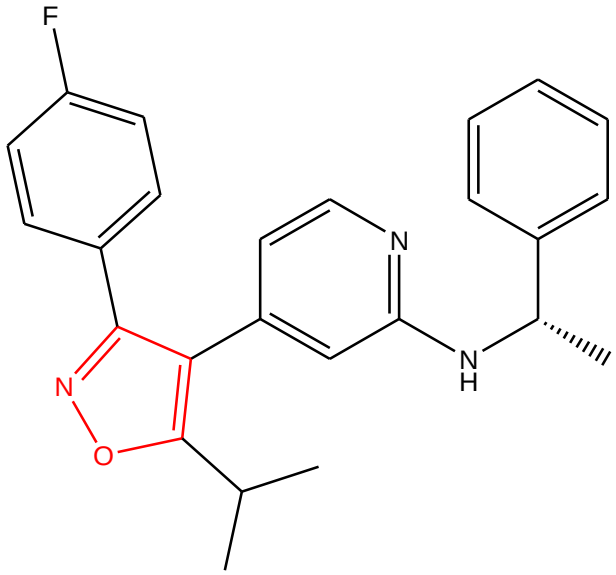


5-(2,4-dichlorophenyl)-3-methylisoxazole

10

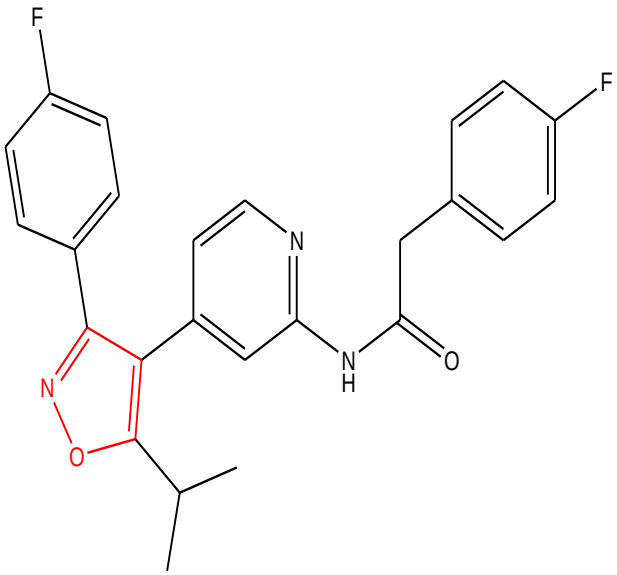
3,4-diaryl isoxazoles were produced by Peifer et al. as a dual inhibitor of p38 MAP kinase & CK1. Compounds 11 and 12 (Figure.1) were discovered to be highly effective p38 and CK1 dual inhibitors[26]. In severe inflammatory disease such as rheumatoid arthritis, asthma, & autoimmune disorder, p38 MAP kinase play a key role in signal transmission (Peifer et al. [27].

Laufer et al. prepared and tested 3,4&4,5 disubstituted & 3,4,5-trisubstituted isoxazoles[28].



4-(3-(4-fluorophenyl)-5-isopropylisoxazol-4-yl)-*N*-((*S*)-1-phenylethyl)pyridin-2-amine

11



2-(4-fluorophenyl)-*N*-(4-(3-(4-fluorophenyl)-5-isopropylisoxazol-4-yl)pyridin-2-yl)acetamide

12

2.2.1. Mechanism of action of anti inflammatory activity

Several novel concepts Tosynthesise 3-methylisoxazol-5(4H)-one/2-hydroxy/mercaptobenzoic acid, o-phenylenediamine and p-amino benzoic acid were utilised. derivatives of -6-methylpyrimidin-4 (5H) One-third-methyl is replaced for -1H-pyrazol-5(4H)-one. - The 1 derivatives of benzimidazoles 5–16 were synthesised using a

hybrid technique and a multi-step synthesis. To screen all test compounds for analgesic and anti-inflammatory properties, the tail flip method, carrageenan induced foot paw edoema technique, & agar streak dilution method were utilized, and in vitro antibacterial properties. The ulcerogenicity of most active substances was investigated using the pylorus ligation procedure. The link between the test substances' chemical structure and their biological activity was studied. 4-(2-(4-(1H-benzimidazol-2-yl)phenyl)hydrazono)-1-(4-(1H-benzimidazol-2-yl)phenyl (4-chlorophenyl) -3-methyl is one of the chemicals that was investigated. The most powerful compound was discovered to be -1H-pyrazol-5(4H)-one 10.

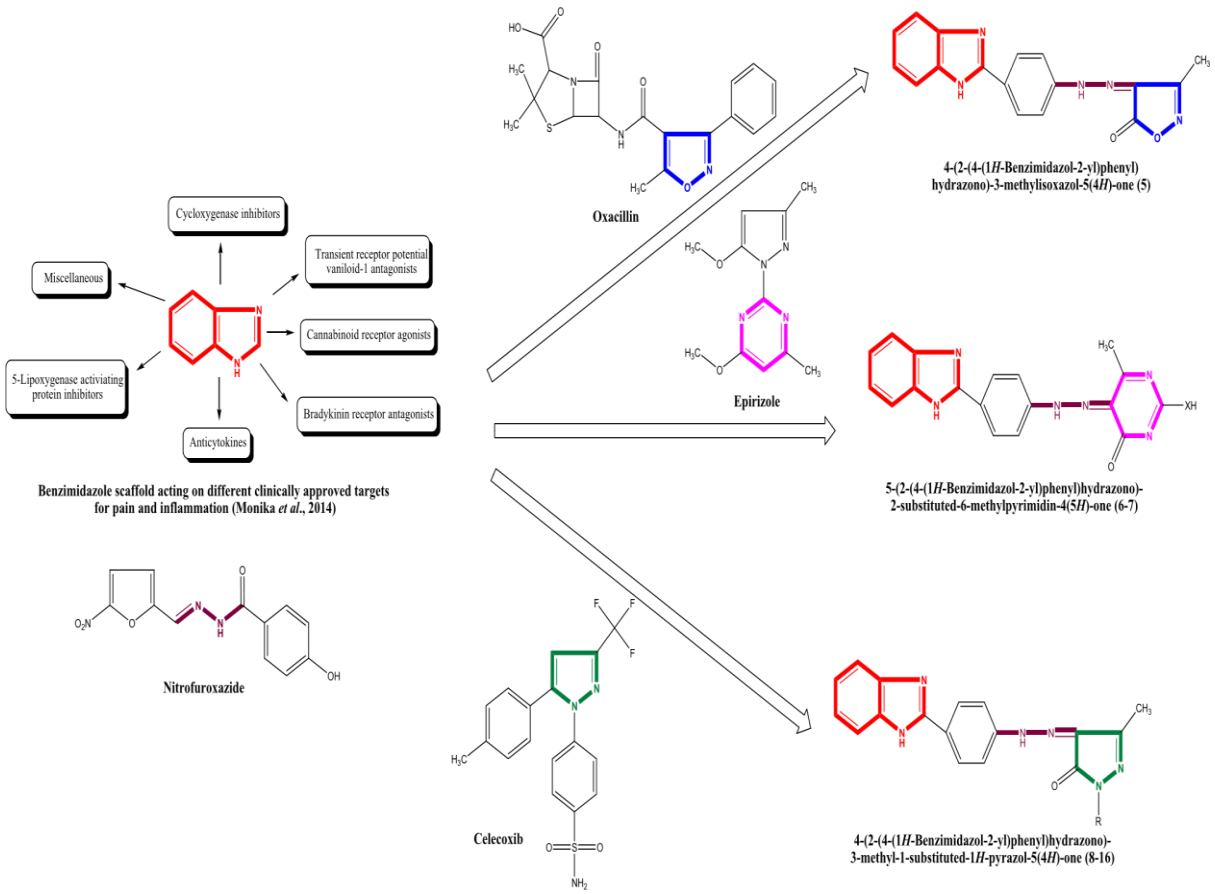
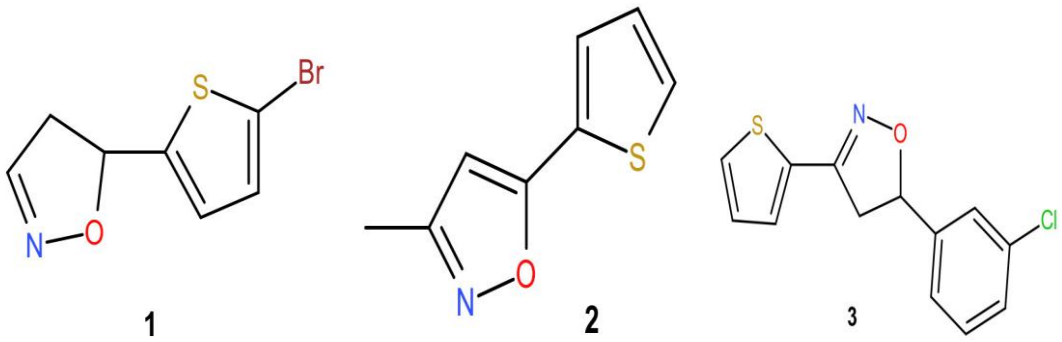


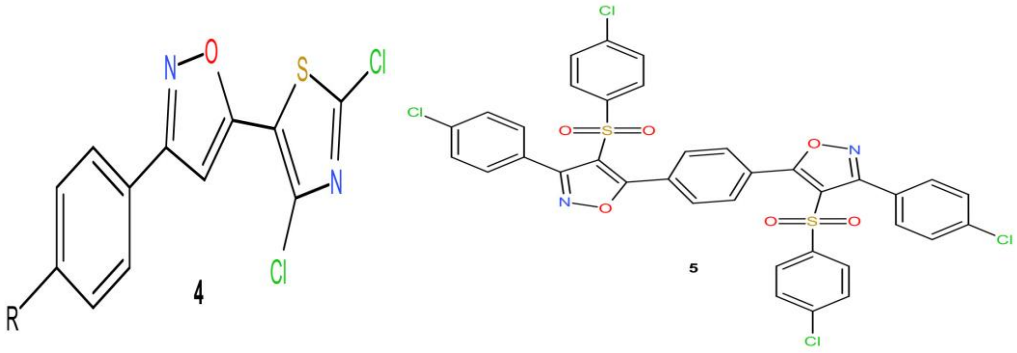
Figure 4 : Mechanism of action of anti inflammatory activity

2.3. Antimicrobial activity:

RamaRao et al. synthesised 5-(heteroaryl) isoxazoles & tested their antibacterial efficacy against E.coli, S.aureus, & P.aeruginosa. Significant activity was observed in isoxazoles substituted with 2-thienyl (1; Fig. 1) or 5-bromo-2-thienyl moieties (2; Fig. 1) in the 5-position [29]. Gautam and Singh (2013) synthesised a series of 4,5-dihydro-5-(substitutedphenyl)-3-(thiophene-2-yl) isoxazoles, utilizing the disc diffusion technique, which were then examined in vitro for antimicrobial activities against S.aureus, B esubtilis, E.coli, and P. aeruginosa, as well as antifungaleactivity against A.niger and C. utilizing the disc diffusion technique, which were then examined in vitro for antimicrobial activities against S.aureus, B.esubtilis, E.coli, and P.aeruginosa, as well as antifungaleactivity against A.niger & C.albicans. The compound 3 (Figure. 1) was shown to be particularly effective against E.coli, P.aeruginosa, and C.albicans given the presence of chloride on the aromatic ring. This may be due to its increased lipid solubility albicans. The compound 3 (Fig. 1) was shown to be particularly effective against E.coli, P.aeruginosa, & provided that the aromatic ring contains chloride This might be because to its higher lipid solubility. [30].

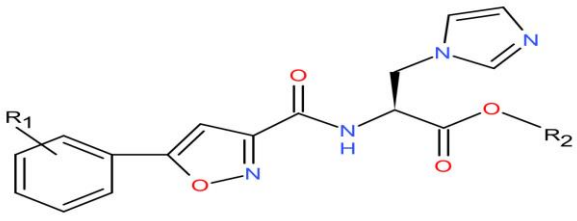


Basha et al. synthesised thiazolyl isoxazoles and tested their antibacterial, antifungal, and antibacterial activities against S.aureus, B.subtilis, K.pneumoniae, & P.aeruginosa. S. aureus and A. niger were shown to be susceptible to thiazolyl isoxazoles with a phenyl ring (4; Fig. 1) replaced with chloro and nitro[31]. The aromatic ring has been swapped with chloro. (5; Fig. 1) The (1,4-phenylene)bis(arylsulfonyl isoxazoles) line regenerated by Lavanya et al. demonstrated strong antibacterial activity (38mm at 100g/mL) against B.subtilis, whereas the remainder of the products inhibited spore germination against P.chrysogenum & A niger. [32].



4 5

Zhao et al. (2017B) developed a variety of aromatic heterocyclic compounds and tested them for antifungal activity in vitro. Compounds with an isoxazole nucleus (6; Fig. 1) showed better efficacy against Aspergillus spp. And compounds with a fluoro substituent at the 2-position of the aryl moiety showed impressive activity against Candida spp., Candida neoformans, Aspergillus fumigatus, and a fluconazole resistant Candida albicans strain, as well as weak inhibition profiles for various human cytP450 isoforms and excellent blood plasmas tability[33].

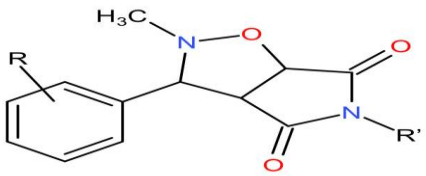


R1=-H,4-CH_3,4-F,4-Br,2-F

R2=$CH(CH_3)_2$,-$CH_2CH(CH_3)_2$

6

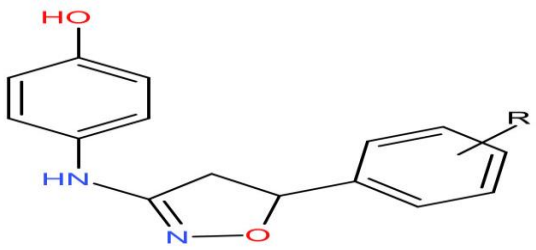
Agirbas et al. synthesised the 2,3,5-substituted perhydropyrrolo[3,4-d]isoxazole- 4,6-diones (7; Fig. 1) by N-methyl-Carylnitronesa were cycloadditioned with N-substituted maleimides and assessed for antibacterial activity. The majority of them were found to be effective against E. faecalis and S. aureus[34].



R=p-NEt_2,p-NMe_2,p-Cl,m-Cl,m-Br,R'=Me,Ph

7

Sahu et al. created a series of novel 4-(5-substituted-aryl-4,5-dihydro -isoxazole-3-yl-amino)phenols (8; Figure. 1) as well as tested them for antibacterial & antifungal activity against S.aureus & S.typhi in vitro. The compound with a 4-Cl phenyl substitution at the 5- position of isoxazole was discovered to be the most effective antibacterial and antifungal agent in the series[35]



R=-H,4-NO_2,4-OCH_3,2-OH,4-Cl

8

2.3.1. Mechanism of action of anti-microbial activity

The fatal impact of nanocomposites on bacteria began with breakdown of the bacterial membrane, followed by cellular internalisation of the nanoparticles and inhibition of intracellular enzyme activity, according to the antimicrobial mechanism. In diabetic rats, this new antibacterial substance with strong cytocompatibility accelerates wound healing and has a bright future in the treatment of various infectious disorders.

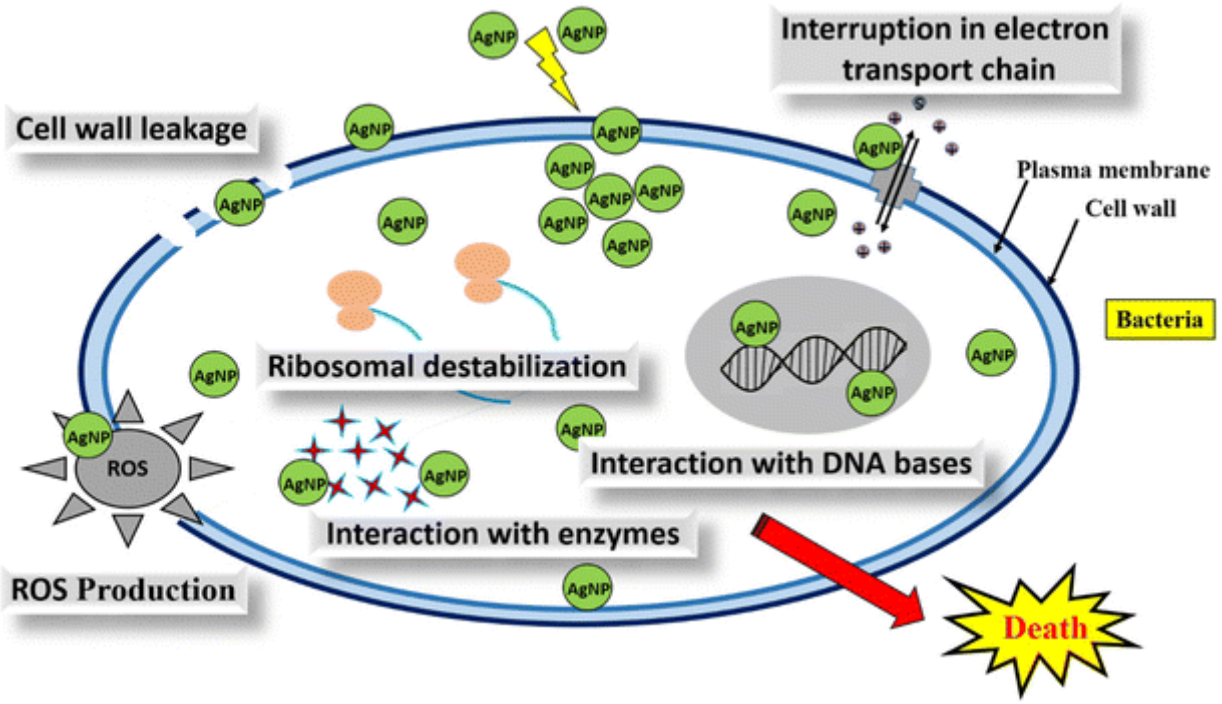


Figure 5 :Mechanism of action of anti-microbial activity

2.4. Antioxidant Activity

The antioxidant activity of synthesised compounds 2a–2g was determined. Each chemical was produced as a 1 mg/ml solution by dissolving 1 mg in 1 ml of methanol; this stock was then methanol dilution to obtain varied amounts (2 g/ml, 5 g/ml, 10 g/ml, 20 g/ml, 50 g/ml, and 100 g/ml). 1 ml of every concentration was combined with 1 ml of methanol & 1 ml of a 2,2-diphenyl-1-picrylhydrazyla (DPPH) solution. In the dark, the solution was incubated for 30 minutes at room temperature. To produce a solution with blank, the plant part was replaced with methanol. [36]. As a positive control, Trolox was employed. A UV-Vis spectrophotometer was used to measure the absorbance at 517 nm, and the results were compared to the control. The following equation was used to determine antioxidant activity:-

I(%)=[ABSblank-ABStest]/[ABSblank]*100%

ABS is the absorbance at 517 nm, and I (percent) is the % antioxidant activity. BioDataFit 1.02 (data fit for biologists) was used to compute the antioxidant IC50 with each synthesized sample chemical [37]. The DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) free radical assay, which generates a violet solution in ethanol, is an antioxidant test based on electron

transfer. The appearance of an antioxidant molecule limits the thermally stable free radical, resulting in a colorless ethanol solution. The DPPH test is a simple and rapid spectrophotometric method for evaluating antioxidants, and it may be used to investigate many products at once. The purpose of this study was to evaluate the antioxidant property of chalcones and pyrazolines using the DPPH free radical assay. The antioxidant properties (AA percent) of all of the compounds was determined using the DPPH free radical assay. Brand-Williams et al. developed a method for determining the radical scavenging activity of DPPH. The samples were subjected to a viable DPPH radical in an ethanol solution. [38]

2.4.1. Mechanism of action of anti-oxidantactivity

When the body's defence (healing) systems become inadequate, reactive oxygen species (ROS) produced by endogenous and external sources can cause oxidative damage and buildup of proteins, lipids, and DNA. These ROS also affect signal transduction pathways, resulting in organelle damage, alterations in gene expression, and altered cell responses, all of which contribute to ageing.

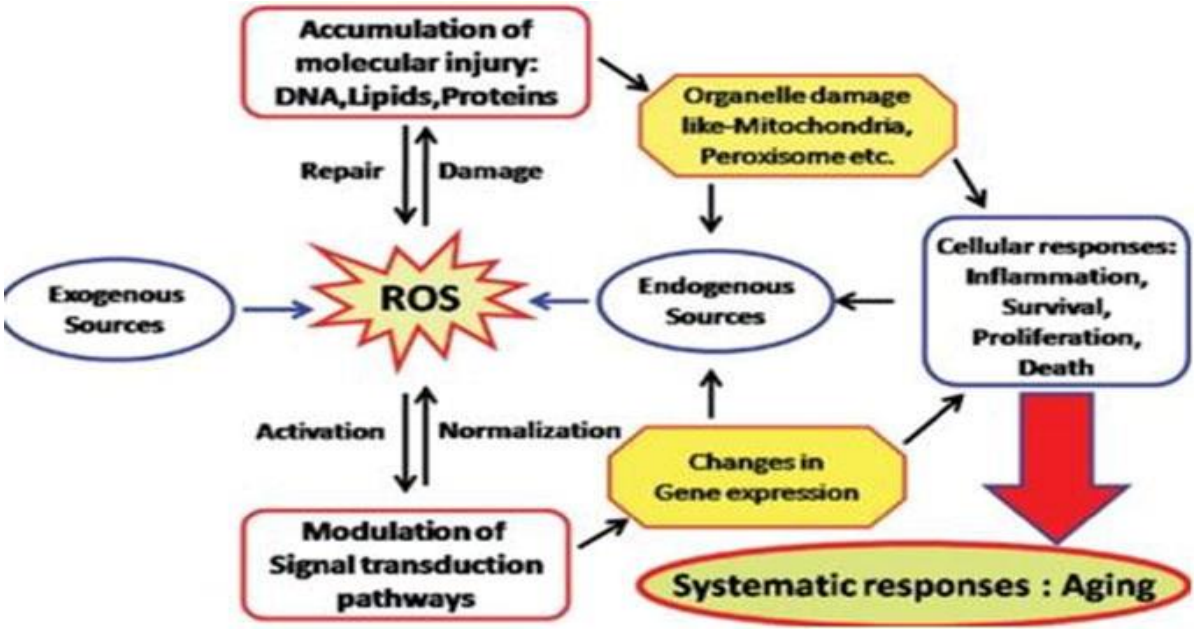
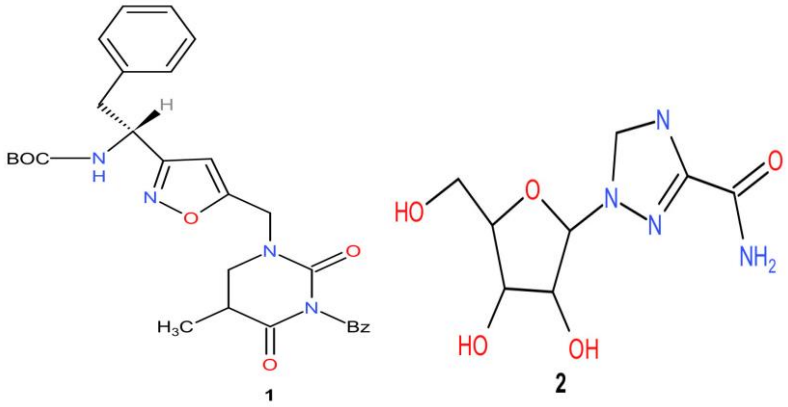


Figure 6 :Mechanism of action of anti-oxidantactivity

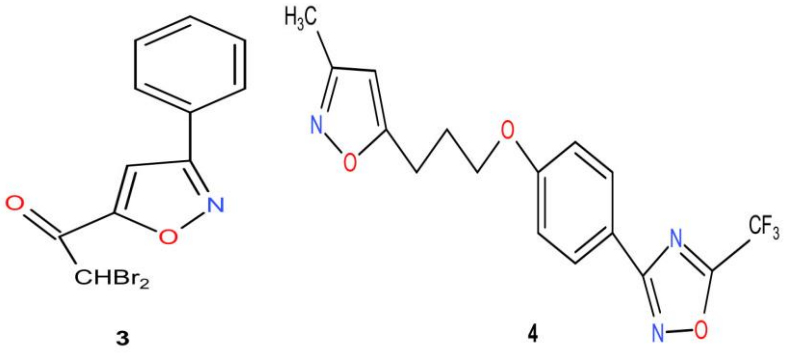
2.5. Antiviral agents:-

The bulk of contemporary antiviral medications act by preventing the replication of viral genetic material.

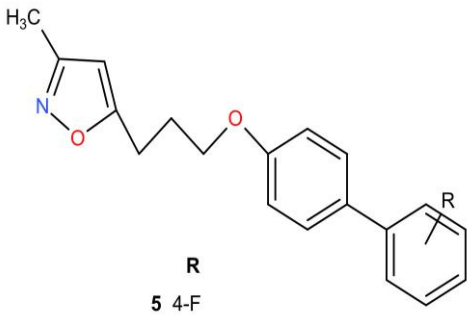
Lee at el. [39] created a series of nucleoside analogues with isoxazole replacing the ribose molecule. The antiviral action was shown to be dependent on protection patterns at the N 3 of the pyrimidine base and the amino site of the chiral carbon. The most desirable protection moieties were bulky protection moieties like Boc or benzoyl. The antiviral effects were significantly reduced when both nitrogen sites were completely deprotected. Derivative 1 (Figure 1) displayed the best activity profile, with a larger anti polio efficacy (EC50 10.61 g/ml) than the reference medication ribavirin 2 (EC50 92.45 g/ml), but a lower selectivity index (SI).The union of a target cell and viral membranes, which is mediated by gp 120, is a critical step in HIV pathogenesis. The synthesis and biological activity of a variety of 2-isoxazolines, isoxazoles, and phenyl ethanes were described bySrivastava et al. [40].



Isoxazole derivative 3 has very high anti HIV activity, which was validated among the derivatives with the greatest spermicidal action. At a dosage of 25 g/ml, this chemical decreased the generation of multinucleated cells (Syntia) by 95% in an HIV 1 glycoprotein mediated cell to cell fusion bioassay, showing its potential as a lead structure for developing derivatives that limit HIV sexual transmission.Picornaviruses, which include enteroviruses and rhinoviruses, are among the most prevalent In humans, they are the cause of respiratory illness as well as fatal neurological and cardiac diseases. Pleconaril (4), a trifluoromethyl oxadiazole derivative, is an effective treatment for these infections. There are still serotypes resistant to pleconaril, despite its strong oral absorption and efficacy against a wide range of enteroviruses and rhinoviruses.



Makarov et al. [41] examined the synthesis & antiviral activities of [(biphenyloxy) propyl] isoxazole derivative made from substituting a phenyl ring for the oxazoline ring in MANUSCRIPT APPROVED ACCEPTED MANUSCRIPT pleconaril. Small electronegative moieties like F, CF3, and Me in the benzene ring, as found in 5, 6, and 7 derivatives, were linked to the highest activity against pleconaril-resistant coxasackievirus B3 Nancy (CVB3 Nancy), pleconaril-sensitive clinical CVB3 isolatea97-927a (CVB3 97-927), as well as living person rhinovirusa2 (HRV2) (HRV-2). Antiviral activity was decreased in compounds such as 4-Phe, 4-OCF3, and 2,3 (1,4)butadiene, on the other hand. Based on the findings of the cytopathic effect inhibitory assay (IC50) and cytotoxic assay (CC50- 50 percent cytotoxic concentration) in HeLa cells, the selectivity index (SI) was determined as the ratio of the CC50 and IC50.Compound 5 had SI values of >37.3 and >5555 in CVB3 97-927 & HRV 2 infected cells, 2.9 and 230.0 in compound 6 , and 2.6 and 57.5 in compound 33, respectively.



R

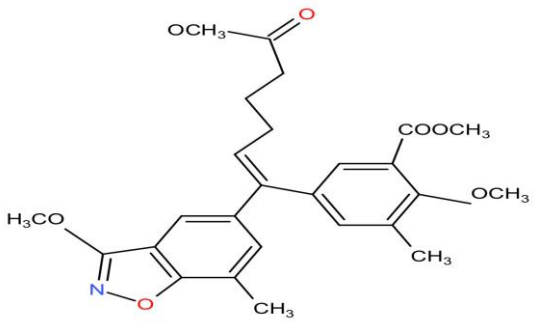
5 4-F

6 3-F

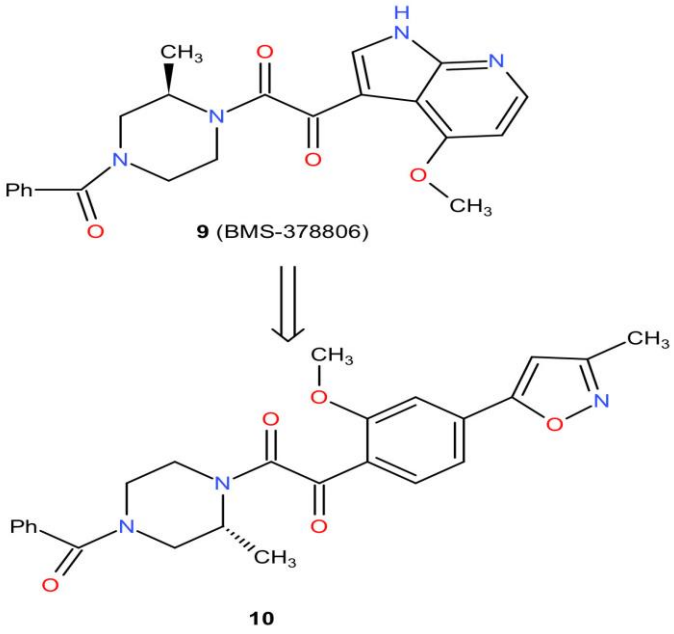
7 2 Me

In the synthesis of alkeny diarylmethanes (ADAMs) containing the benzo[d] isoxazole ring, Deng et al. [42] Stille cross-coupling of a vinylstannane with only an aryl halide was used. The methyl ester group of ADAMs, which is prone to metabolic inactivation, was

substituted with this moiety. Compound 8, which inhibited HIV 1 non nucleoside reverse transcriptase at 0.91 M, had the most intriguing features. Furthermore, at 40 nM and 20 nM, it decreased the virus's cytopathic impact in CEM SS and MT 4 cells, respectively. Because these levels were not cytotoxic, ADAM 3 has a high therapeutic index. When the alkenyl side chain was substituted with an oxazolidinonyl moiety, the antiviral activity of this compound was dramatically diminished. The trans position of the main chain in the benzo[d]isoxazole ring was also preferable to the cis position. Other derivative, 9, was created by substituting the azaindole ring in the molecule of BMS-378806 with an isoxazole moiety (10). It was a powerful inhibitor of the binding of HIV-1 envelope glycoprotein glycoprotein to the infected cells receptor CD4, which is a vital ingredient in HIV infection, just like the parent chemical. [43].This drug has an IC50 of less than 5 nM and similar selectivity to BMS-378806 in a pseudotyped antiviral experiment against virus samples taken from sick people. Viroporins are a protein family whose inhibition is thought to be a promising antiviral therapeutic target . These family of ion channels affects viral entrance, assembly, and release from infected cells. The A/M2 proton channel of the influenza virus, which infect 10-15% of the US population each year and poses a severe treatment challenge, is one type of viroporin.



8

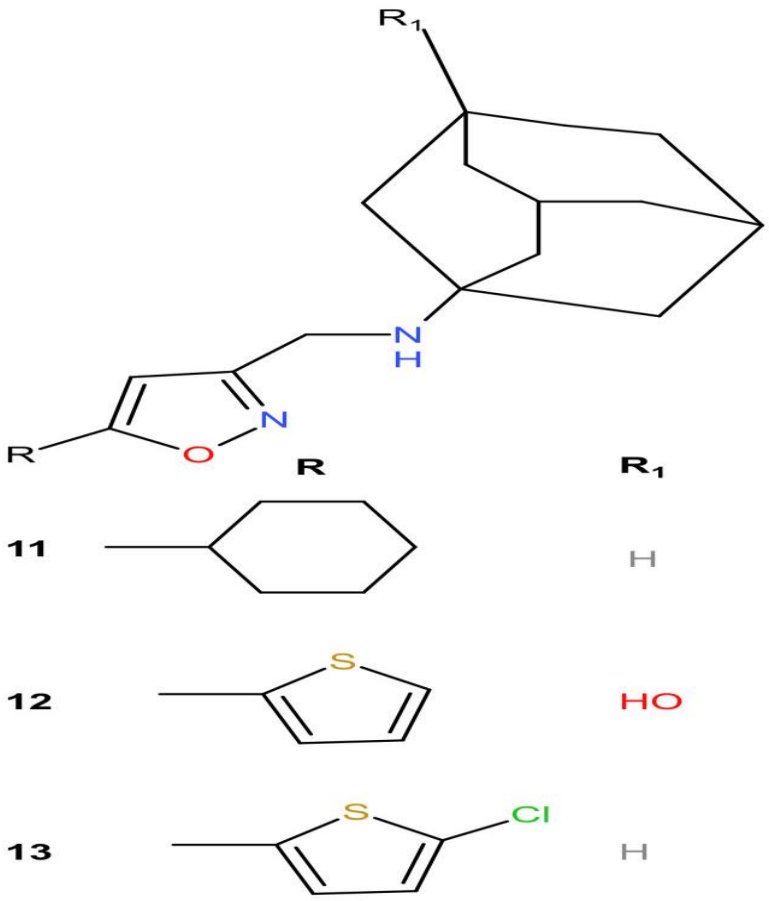


Li et al. [44] To increase their toxic and physical properties, as well as their inhibitory activity against by the A/M2 proteins of the substance S31N form of the transmissible influenza A virus, researchers developed a range of adamantyl-1-NH2 +CH2 –aryl derivatives. All substances were tested in order to inhibit WT and S31NM2 at a concentration of 25 M. S31N inhibition involves the existence of a second amine group. Isoxazole derivatives were likewise more active than 1,2,4-oxadiazole-ring derivatives. Propyl, isopropyl, and cyclopropyl aryl groups 5 substituents have decreased efficacy against WT M2.

Compound 11, At the 5 position of the isoxazole ring, there is a cyclohexyl moiety, has the best capacity to inhibit S31N. At 100 M, it blocked the M2-S31N channel in 90% of cases. In the plack reduction experiment, the 3-hydroxyadamantane derivatives 12 with such a thienyl ring at the 5′ end of the isoxazole were the most active. Plaque formation was 40% at a concentration of 1 M (defined as the percent of plaques number in the present of compound dividing by plaques numbers in the absent of compounds), suggesting that EC50 value were less than 1 M.

In addition, 12 had a selectivity index for mammalian cell that was twices as high as the % drug (>200), indicating that it might be utilised therapeutically. . In addition, 12 had a selectivity index for mammalian cells that was twice as high as the parent drug (>200), indicating that it might be utilised therapeutically.

Another investigation by Li et al. [45] found that compound 13 had the strongest antiviral activity among the isoxazole-containing AM2-S31N inhibitors, with EC50 values of 0.1-0.2 M against all 4 influenza A viruses studied, includes oseltamivir-resistant strains. This derivative was also well tolerated by MDCK cell (CC50-190.5M) & human epithelial A549 cells (CC50-208.6M).



2.5.1. Mechanism of action of anti-viral agent

Antiviral agents can strengthen a cell's resistance to a virus (interferons), limit virus adsorption, diffusion, and deproteinisation in the cell (amantadine), and block nucleic acid synthesis (antimetabolites).

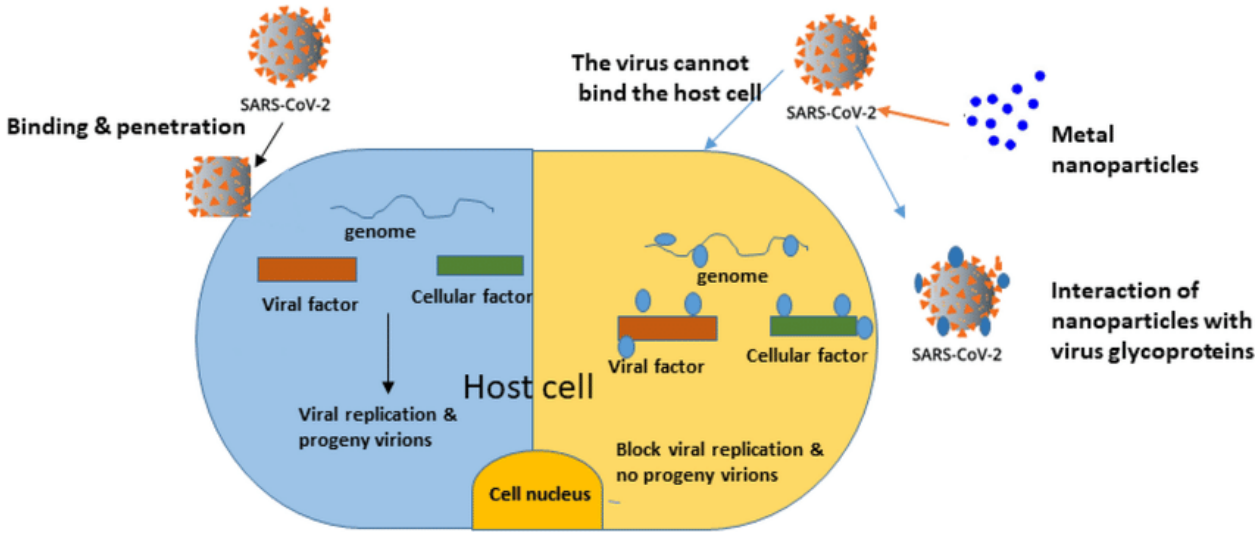
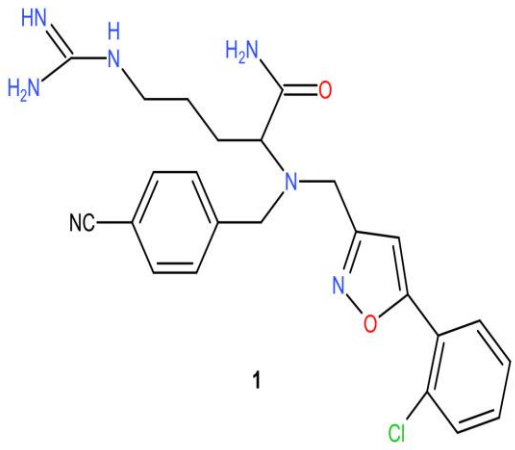


Figure 7 :Mechanism of action of anti-viral agent

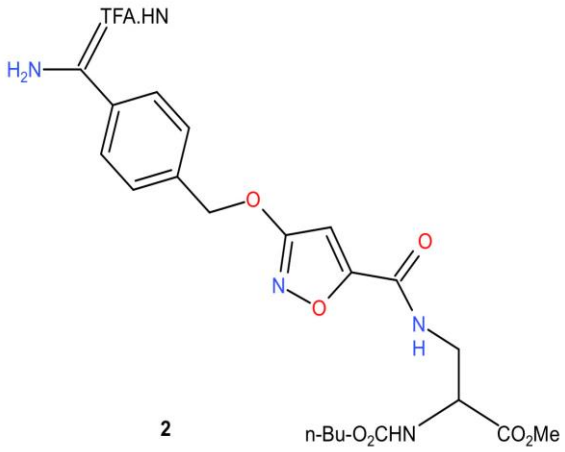
2.6. Antiplatelet, antithrombotic & anti triglyceride agents

Batra et al. [46] used 3-substituted phenyl-5-isoxazolecarboxaldehydes for combinational synthesis of library of isoxazole derivatives. After collagen and adrenaline infusion, antithrombin activity in vivo demonstrated that compound 1 had the best protective potential against thrombotic challenge (Figure 1). In comparison to the control, it also increased bleeding time by 87.5 percent. The inclusion of a 2-chlorophenyl group was required for the maximum activity, while the presence of a simple phenyl or 4 methylphenyl moiety had no influence on the compounds' performance. Platelet aggregation is mediated by glycoprotein IIb/IIIa (GPIIb/IIIa), a membrane-bound protein with a fibrinogen affinity. GPIIb/IIIa antagonists are appealing target inthe hunt for novel antithrombotic medicines to avoid myocardial infarction, angina pectoris, or stroke. Benzamide series of GPIIb/IIIa inhibitor with impressive in vitro antiplatelet effect but capacity to block ADP induced platelet aggregation in-vivo in dogs were reported by Xue et al. [47].



1

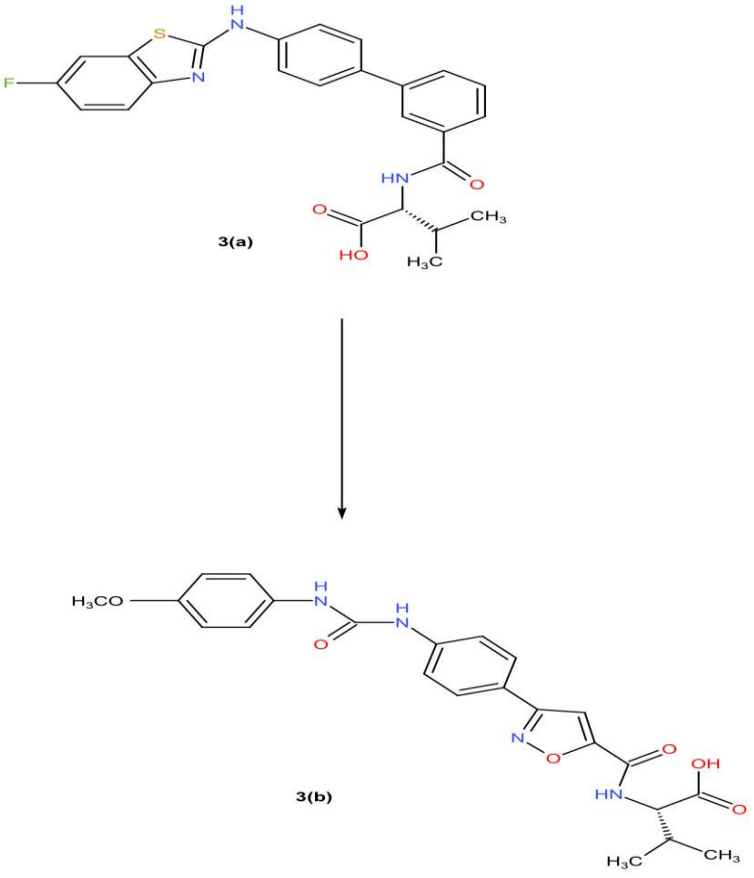
Compound 2 (Figure 1) was made by substituting the benzamide group in the most effective derivatives with isoxazole carboxamide, which demonstrated improved antiplatelet activity in dogs dependent on the dose administered oral (platelet aggregation inhibitory activity of 60% at 0.8 mg/kg). Triglyceride synthesis is aided by the enzymes diacylglycerol acyltransferase 1 (DGAT1). Its inhibitors might be useful in the treatment and prevention of metabolic disorders such dyslipidemia, obesity, and 2 diabetes.



2

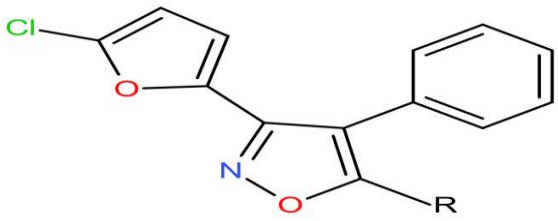
As DGAT1 inhibitors, Jadhav et al. [48] produced a variety of 3-phenylisoxazole, 5-phenyloxazole,& 3-phenyl-1,2,4-oxadiazole derivative. The compounds with the 3-phenylisoxazole scaffold had the greatest solubilites & DGAT1 inhibitores activity in an in vitro enzymatic testing. In addition, urea linkers with three units were preferred above thiourea, sulfonylurea, 2 hydroxyacetamide, oxalamide, amide, sulfonamide, & ether linker. In addition, the addition of the 4-methoxy moiety to the . In comparison to chloro, fluoro, methyl, and trifluoromethyl analogues, structure had a positive impact on compound activity and solubility. The greatest profile of action linked to high oral bioavailability was

established for derivative(3b) (Figure 1), which lowered triglyceride levels by 90% in mice in an acute in vivo fat tolerances test [FTT] at a dosage of 3 mg/kg. It was equally efficient as the parent chemical fluorobenzothiazole biphenyl acid (3a), but (3b) had a substantially higher water solubilites of 0.43 mg/ml (compared to 0.01 mg/ml in the parent drug).COX-1 is a cytoprotective prostaglandin (PG)E2 synthase enzyme that is produced constitutively in the majority of mammalian cells. It also plays a role in the production of proaggregatory thromboxane (TX) A2 in platelets. COX 1 has a role in the development of thrombosis, atherosclerosis, and carcinogenesis under pathological circumstances. This finding suggests that selective COX-1 inhibitors might be effective in the preventions and treatments of certain cardiovascular diseases.



As COX 1 inhibitor with antiplatelet action, Vitale et al. [49] developed a novel class of 3,4-diarylisoxazoles. The presence of an isoxazole ring & a furanyl groups in the structure of compound was linked to high COX 1 selectivity. The substitution of a bromo or methyl moiety in the furyl core of the parent chemical 4 (Figure 1) instead of a chloro group, as well as the replacements of the 5 methyl moiety with CF-3, resulted in greater COX-1 binding of the derivatives. Compound 5 had the highest selectivity toward COX-1, being >100 times

more powerful to inhibit COX 1 (IC50- 0.81M) than COX 2 (IC50 >100M) and inhibiting human platelet aggregation as well as TXA-2 production in responses to proaggregatory stimuli.



4:CH_3
5:CF_3

2.7.1. Mechanism of action of anti- antithrombotic agent

Stimulation of the coagulation system & platelets are necessary for the formation of arterial and venous thrombi, despite their distinct causes. TF(tissue factor) exposure at sites of atherosclerotic plaque rupture is the most common cause of arterial thrombosis. In venous thrombosis, on the other hand, the vein wall is generally intact. Endothelial cells lining the vein become activated and produce adhesion molecules in response to decreased flow, hypoxia, or inflammatory mediators, which tie TF-expressing leukocytes and microparticles to their surface.Extrinsic tenase is formed when TF binds to and activates factor VII (factor-VII). FX (factor-X) & FIX (factor-IX) are activated by this compound (factor-IX). On the surface of active platelets, FIXa (factor IXa) binds to FVIIIa (factor-VIIIa) to generate intrinsic tenase, which turns on FX. FXa (factor Xa) binds to Fva (factor Va) on the surface of active platelets to create prothrombinase, which converts prothrombin to thrombin. Thrombin converts soluble fibrinogen to fibrin, activates FXIII (factor XIII), which cross-links the fibrin, and stimulates its own production by stimulating FV (factor V), FVIII (factor VIII), and FXI (factor XII) (factor XI).Thrombin is also a powerful platelet activator, and the burst of thrombin produced at injury sites increases platelet activation and aggregation.Platelets that have been activated serve as procoagulants in at least two ways. To begin, active platelets offer an anionic phospholipid surface on which clotting components assemble, which is required for effective thrombin

production. Second, active platelets produce inorganic polyphosphates from their dense granules, which activate the coagulation contact pathway and increase FXI activation by thrombin. As a result, in the onset and propagation of arterial and venous thrombosis, activation of the coagulation system and platelets is critical. HK stands for high-molecular-weight kininogen, whereas PK stands for prekallikrein. With permission, adapted from Fredenburg et al4.

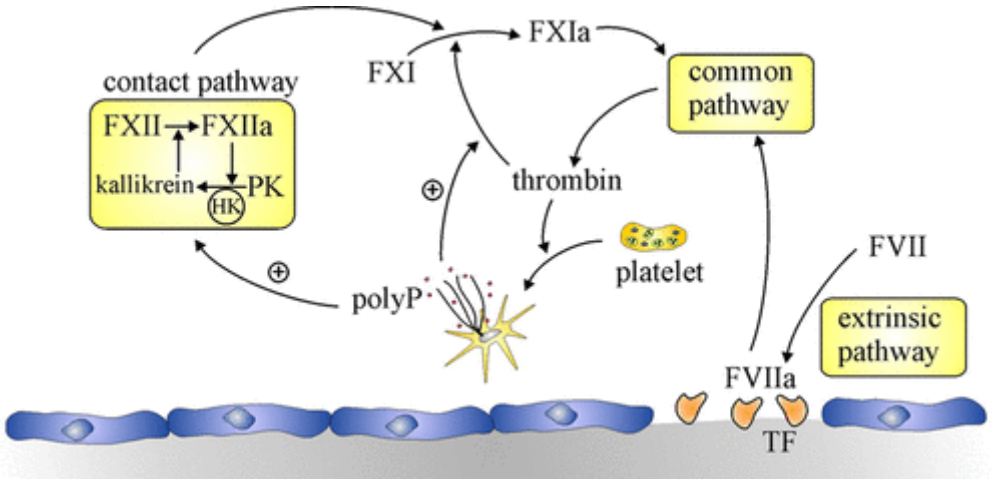


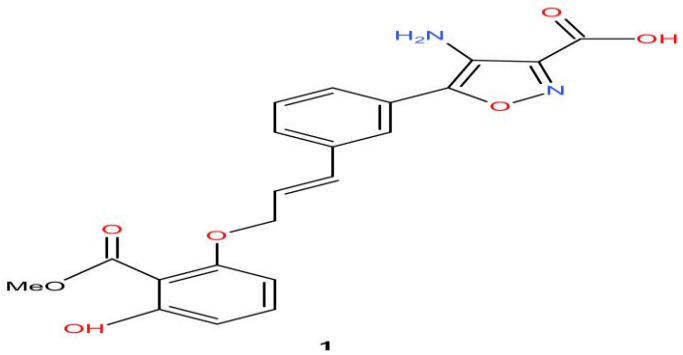
Figure 8 :Mechanism of action of anti- antithrombotic agent

2.7. Anti diabetic agents

One of the therapeutic targets in the search for anti-diabetic medications is protein tyrosine phosphatase 1B (PTP1B), which is critical for down regulation of insulin and leptin signalling pathways..

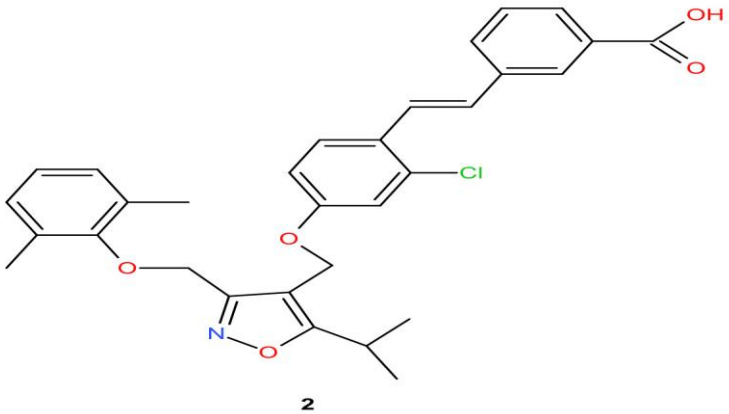
Zhao et al. [50] investigated isoxazole carboxylic acid derivative like as PTP 1B inhibitors using X-ray crystallography-guided SAR. They discovered that PTP1B's catalytic site was hydrophilic, and the optimal interactions with possible inhibitor needed the presence of polar group, which raised the isoxazole carboxylic acid's pKa value and so increased the content in physiological fluids in its neutral state. Derivative 1 (Figure 1), which contained a α - amino in 4th position of the isoxazole ring, a smaller molecular weight and polarity, and showed excellent cell functions against PTP1B in the COS 7 cell line, met these requirements. Another biological target for diabetes medication is the nuclearfarnesoid X

receptor (FXR), which is present in cells of liver, gall bladder, gut, renal, and adrenal glands and is critical for glucose homeostasis & lipid metabolism.



1

Bass et al. [51] To modify the FXR agonistic properties and metabolic stability of GW4064, a well-known chemical, researchers produced a number of forty 3,5-substituted isoxazoles and examined their capacity to interact with FXR. The experiment showed that changing 2 atom in the phenyl ring linking to the isoxazole ring boosted the efficacy of the chemical. The steric nature of these substituents was also more essential than their electronic character, with compound 2 having the highest activity (EC50= 17 nM). It was far more effective than dichloro substituted or trisubstituted derivative, as well as the parent compound. Activation of the G-protein associated receptor 40 GPR40 might be a potential treatment option for type 2 diabetes (T2DM). This free fatty acid receptor is found on the surface of pancreatic -cells and intestinal enteroendocrine cells, and when activated, it causes glucose-stimulated insulin release with little hypoglycemia risk.

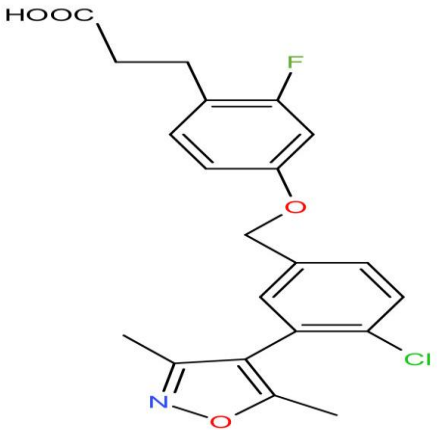


2

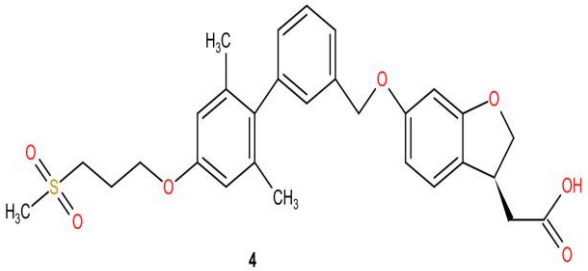
A series of strong GPR40 agonists was identified by Yang et al. [52].

The compounds' polarity was improved and their CNS penetration and toxicities were

reduced when the 2,6 dimethylphenyl group was replaced with 3,5 dimethylisoxazole. The highest in vitro effectiveness was found in derivative 3 with the chlorophenyl moiety (EC50- 15.9nM), which were then tested in vivo.Compound 3 effectively lowered blood glucose level in ICR mice and type2 diabetic C57BL / 6 mices in an oral glucose tolerances test (by 29.5percent at a dosages of 30mg/kg) to a level equivalent to a references compound TAK 875 (4) used in phase 3 clinical trial. In contrast to this derivative , however, 80 appeared to have a lesser risk for CNS harm.

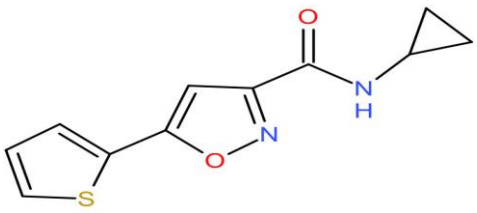


3



4

N-cyclopropyl-5-(thiophen-2-yl)-isoxazole-3-carboxamide 5 is as well a possible method in the growth of innovative anti-diabetic medications. According to Kalwat et al. [53], this medication increased expression of genes that support neuroendocrine & -cell phenotypes while decreasing those that promote cell proliferation, and this activity was attributed to mRNA transcription activation rather than stabilization. As a result of the activation of genes involved in fatty acid metabolism, insulin production, and secretion, -cell function was changed. Furthermore, in the PANIC, 5 enhanced in vivo oral glucose tolerances. ATTAC animal research on -cell repair following ablation.



5

2.7.1. Mechanism of action of anti- diabetic agent

Anti-diabetic medication mechanisms of action. Because of the availability of a wide range

of antidiabetic medicines, the lifetime of type 2 diabetic patients is continuously growing. Multiple processes are used by these medications to lower blood glucose levels. Metformin, a commonly prescribed hypoglycemic medication, works by boosting glucose consumption in peripheral tissues while lowering hepatic glucose production. Sulfonylureas cause pancreatic cells to secrete more insulin. This type of medication has been linked to hypoglycemia episodes. Thiazolidinediones (TZDs) increase insulin sensitivity in adipose tissue, skeletal muscles, and the liver. Incretin treatments that boost pancreatic insulin release include DPP-4-resistant GLP-1 analogues and DPP-4 inhibitors that increase endogenous GLP-1 levels.They are also said to have insulin-independent activities in other tissues, including as the brain. SGLT2 inhibitors, which impede glucose reabsorption in the renal tubules, increase glucose excretion in the urine. Overall, anti-diabetic medications have been demonstrated to have favourable effects on the brain, either directly or indirectly through glycemic management

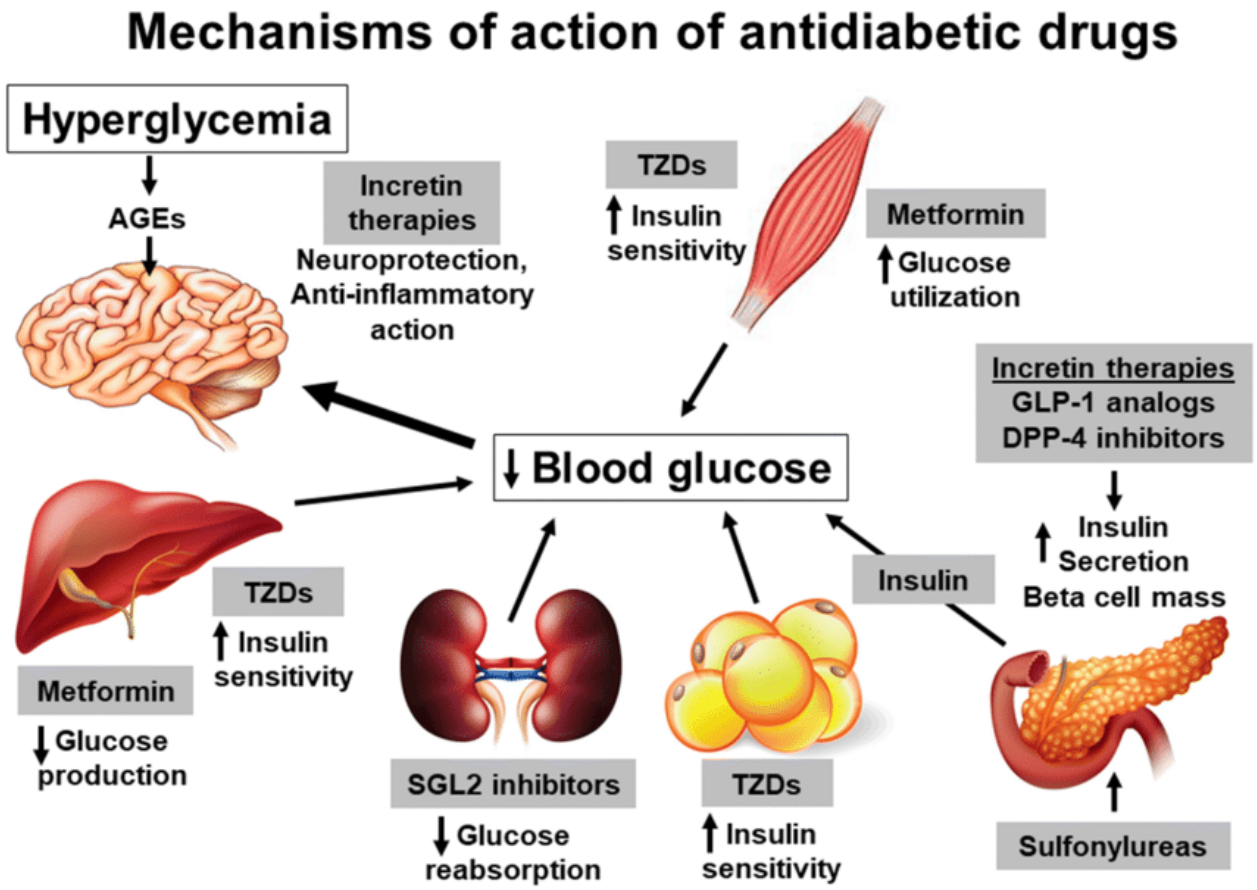
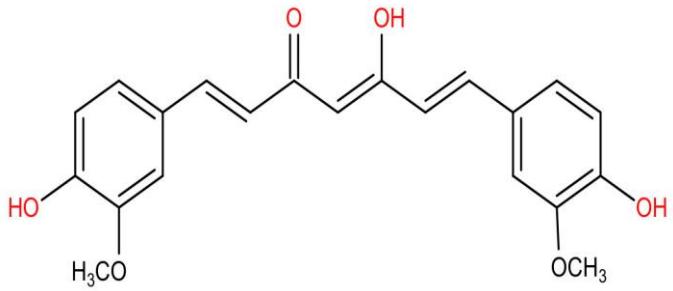


Figure 9 :Mechanism of action of anti- diabetic agent

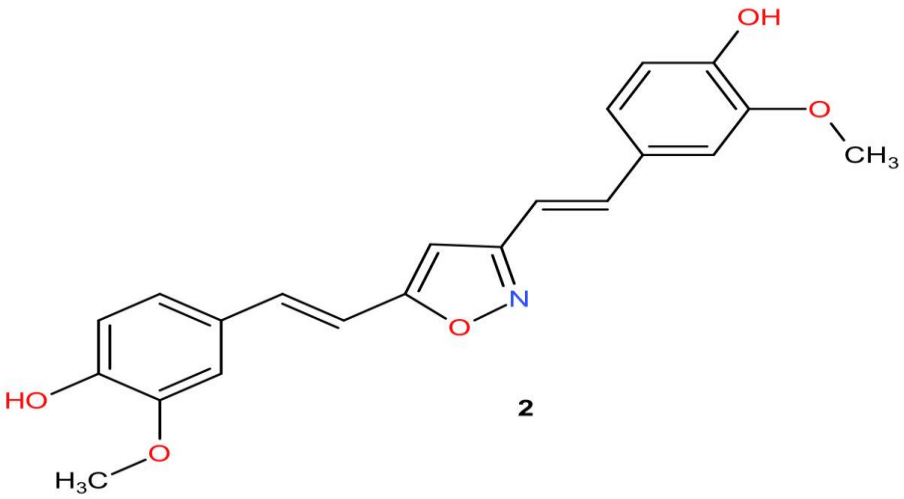
2.8. Anti Alzheimer agents

The extracellular accumulation of aggregate amyloid (A) peptides and neurofibrillary tangles produce Alzheimer's disease (AD). One of the substances that attaches to A and inhibits the metabolism of the amyloid precursor protein is curcumin (1). (APP).



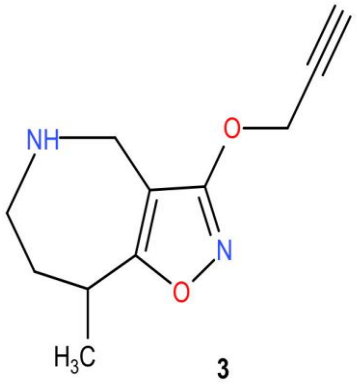
1

Narlawar et al. [54] substituted the 1,3 dicarbonyl moiety in curcumin with heterocycle like as isoxazole & pyrazole to lower curcumin's susceptibility to metal chelation and increase it's affinity for A aggregate, resulting in a variety of strong .A secretion inhibitors. They operated at different points along the amyloid cascade. The isoxazole derivative 2 had the most intriguing features, as it greatly reduced the activity of -secretase, which is responsible for the essential step of A release from the organic membrane. Specifically, the APP trans-membrane domain ultimate cleavage. The function of cholinergic neurons is also disrupted by Alzheimer's disease, resulting in a cholinergic neuropathy.Patients' cognitive capacities may be improved by pharmaceutical activation of muscarinic receptors.The sickness has harmed me. In this mechanism, postsynaptic M-1 receptor in the brain plays a critical role.



2

To improve M1-selectivity, Lenz et al. [55] changed the structures of previous known isoxazolo[4,5-c]azepine muscarinic agonist. The substitution of the 3methoxy group with the 3propargyloxy moiety in the bicyclic structures was shown to increase muscarinic affinity. Furthermore, while the addition of the methyl group at position 8 reduced the effectiveness of derivative 3, it increased its M-1-selectivity (EC50- 1300nm for M-1 receptor, EC50>51000nm for M-2 receptor). This might imply a lesser probability of negative side effects from M2 agonism after in vivo treatment.



3

4-ethyl-5-(pentan-2-yl)-3-(prop-2-yn-1-yloxy)-1,2-oxazole

2.8.1. Mechanism of action of anti- Alzheimer agent

Crocus sativus extracts may have an anti-mechanism Alzheimer's of action. CSE improves A clearance through the BBB, tightens the BBB to prevent undesirable big molecules from entering, and has an anti-inflammatory impact by lowering astrocyte activity and brain interleukin-1 beta. BBB, Blood-Brain Barrier; CSE, Crocus sativus Extracts; A, Amyloid beta

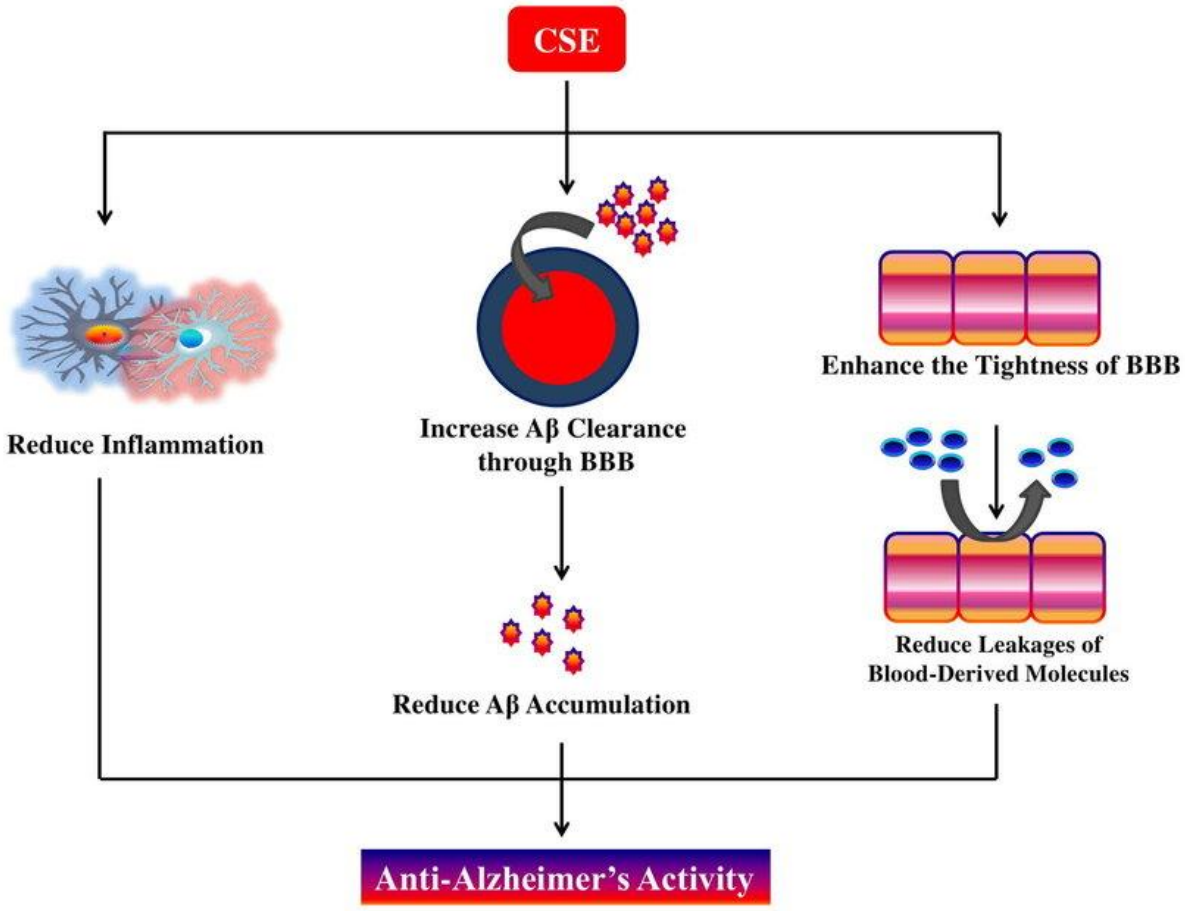
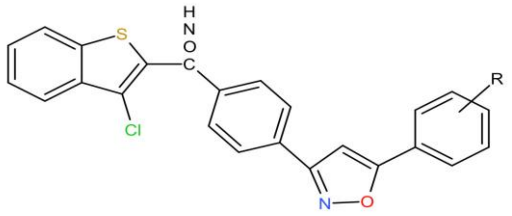


Figure 10 :Mechanism of action of anti- Alzheimer agent

2.9. Antitubercular activity:-

Kachhadiaetal.[56] (2004) developed an seriess of 1-[p-(3′-chloro2′-benzo(b)thiophenoylamino)-phenyl]-5-aryl-isoxazoles sand tested for their antitubercular efficacy. Compound 1a, 1b, & 1c (Figure. 1) were shown to have strong anti-MTB H37Rv action. Using the Lownstein-Jensen MIC approach,

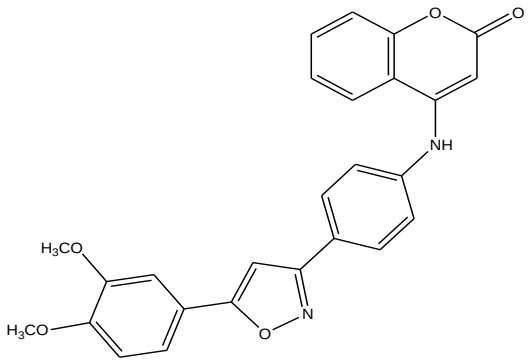


1 **a** R=3-Cl

b R=3,4-$(OCH_3)_2$

c R=4-SCH_3

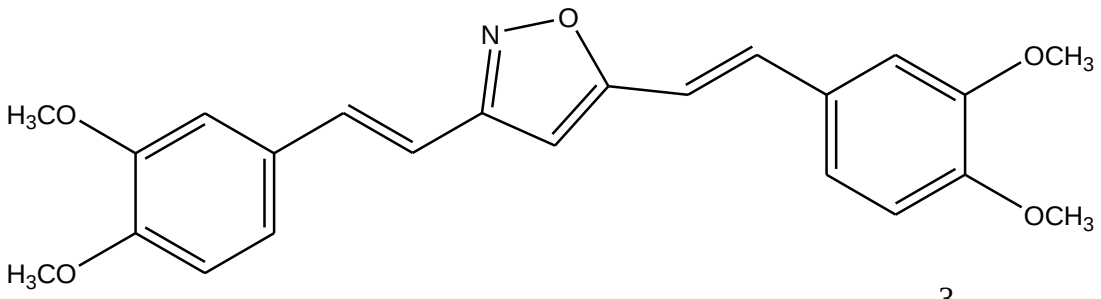
Patel et al. (2014) [57] synthesised coumarin based isoxazole & tested their anti-mycobacterial activity against MTB H37Rv. Compound 2 (Fig. 1), which had a methoxy group, showed strong antimycobacterial action with a MIC of 62.5 g/mL and a 99 percent inhibition rate, whereas the remainder of the compounds had MICs ranging from 100 to 1000 g/mL.



4-(4-(5-(3,4-dimethoxyphenyl)isoxazol-3-yl)phenylamino)-2*H*-chromen-2-one

2

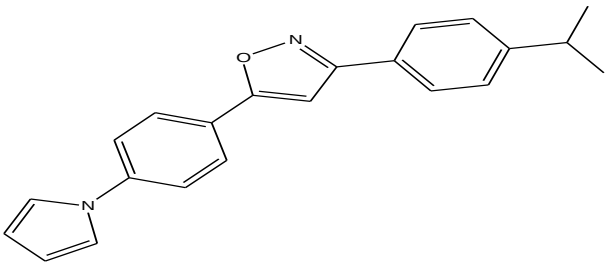
Changtam et al. [58] (2010) created curcumin isoxazole analogues and tested its antimycobacterial activity. On the aromatic ring, the presence of p methoxy & phydroxy group increased the activity. Compound 3 (Fig. 1) was founded to be 1131 fold more reactive than curcumin & roughly 18 & 2 fold more reactive than conventional medications kanamycin & isoniazide, respectivelly. Compound 3 (Figure.1) had hoghly action against MTB clinical isolate that were multidrug-resistant (MIC 0.195–3.125 g/mL).



3

3,5-bis((*E*)-3,4-dimethoxystyryl)isoxazole

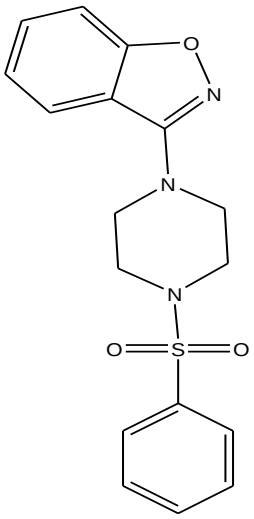
Joshi et al.[59] (2016) created pyrrolyl derivative with an isoxazole moiety & tested them for MTB reactivity. When evaluated for mammalian cells toxicie use as the A-549 cancer cells line, compound 4 (Fig. 1) showed substantial efficacy against the H37Rv strain and was shown to be non-toxic.



4

5-(4-(1*H*-pyrrol-1-yl)phenyl)-3-(4-isopropylphenyl)isoxazole

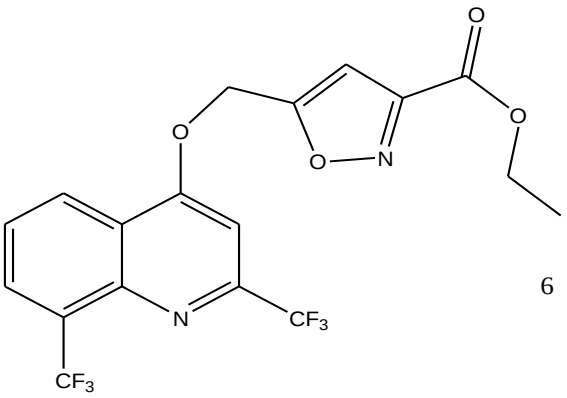
Naidu et al.[60] (2014) created a series of 3-(4-(substituted sulfonyl) piperazin-1-yl)benzo[d]isoxazole analogues & tested their antitubercular efficacy in vitro against the MTB-H37Rv strains. The MIC of all the substances ranged from 3.125 to 50 g/mL.At a concentrations of 3.125g/mL & a selectivity of >130, compound 5 [Fig. 1].) identified as the most potential solution in the series, inhibiting MTB H37Rv development by 99 percent.



5

3-(4-(phenylsulfonyl)piperazin-1-yl)benzo[*d*]isoxazole

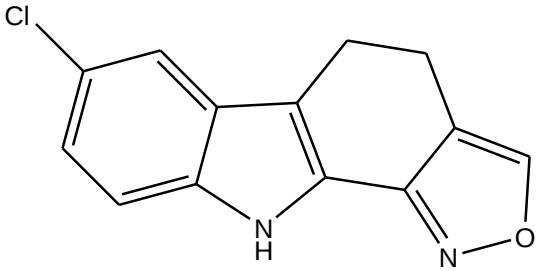
Mao et al.[61] (2010) created carboxylic esters of mefloquine and isoxazole and tested their antitubercular activity.Compound 6 (Fig. 1) was discovered to have good intracellular and extracellular activity and selectivity against MTB H37Rv. Compound 6's ester bio-isosteres were ineffective as antitubercular agents, suggesting that the ester is working as prodrug.



6

ethyl 5-((2,8-bis(trifluoromethyl)quinolin-4-yloxy)methyl)isoxazole-3-carboxylate

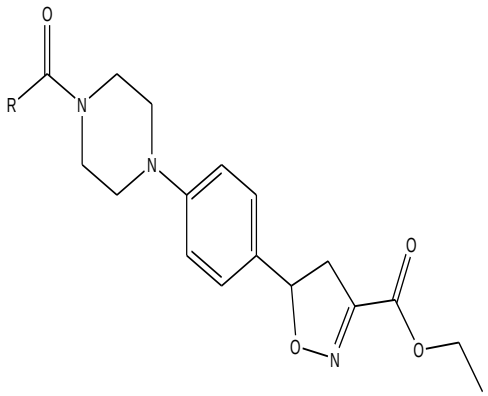
Yamuna et al.[62] (2012) synthesisedisoxazolocyclohepta[b]indoles and tested them for antimycobacterial activity against MTB H37Rv in vitro.Compound 7 (Fig. 1), which has a chloro substituent in cyclohepta [b]indole moiety, had the highest activity. This chemical was discovered to be non-mutagenic, making it biologically safe to consume.



7

7-chloro-5,10-dihydro-4*H*-isoxazolo[3,4-*a*]carbazole

Rakesh et al. [63] (2009) made 3,5 disubstituted isoxazoline ester & tested their anti tuberculosis efficacy. Piperazyl urea (8a; Fig. 1) and piperazylcarbamate (8b; Fig. 1) were used to replace the isoxazoline C-5 position, which increased anti-tubercular action. However, replace the ester group at C 3 with bioisosteric groups result in full activity loss.



8a R=-NH$(CH_2)_5CH_3$
8b R=-OCH_2CH-CH 8

2.9.1. Mechanism of action in Antitubercular activity

Tuberculosis medications hinder cell wall production, protein synthesis, and nucleic acid synthesis, among other elements of Mycobacterium tuberculosis biology. The DNA is affected by PAS, Fluoroquinolones, Cyclic Peptides, and Aminoglycosides.

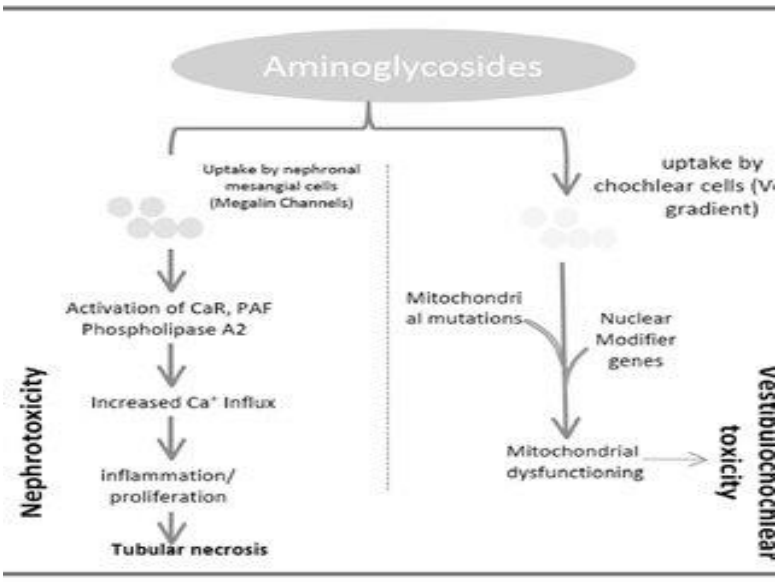
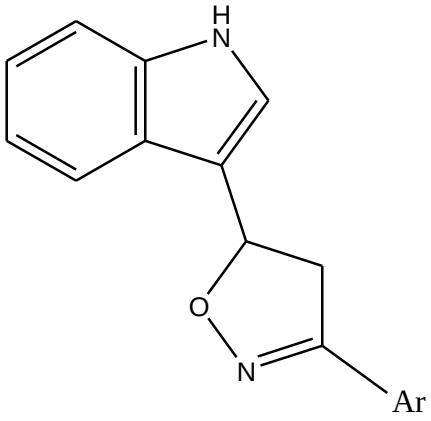


Figure 11 : Mechanism of action in Antitubercular activity

2.10. Antidepressant activity

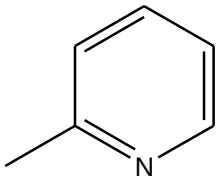
Patil and Bari[64] (2013) synthesisedisoxazolines containing indole and tested them for antidepressant efficacy in mice using a forced swim test and an actophotometer to measure locomotor activity. With no substantial decrease in locomotor activity, all of the drugs demonstrated considerable antidepressant efficacy. When compared to the reference medications imipramine and fluoxetine, compounds 1a and 1b (Fig. 1) appeared as effective

antidepressants, demonstrating that the inclusion of an adequate heterocyclic rings can leads to potent antidepressant. The synthesis of enantiomeric pair of 7-amino3a,4-dihydro 3H-[1]benzopyrano[4,3-c]isoxazole derivative was described by Andrés et al. (2003). [65]



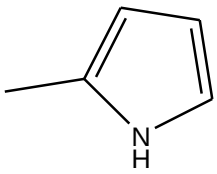
1

Ar=



2-methylpyridine

1a

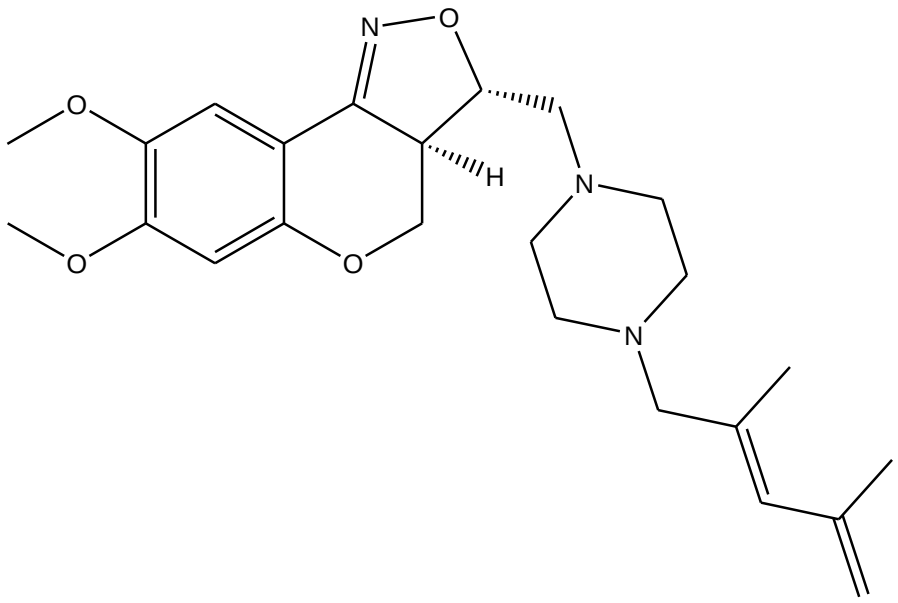


2-methyl-1*H*-pyrrole

1b

Compound 2 (Fig. 1) was shown to be the most effective 2 adrenoceptor blockers, decreasing serotonin(5 HT) reuptake & so functioning as an antidepressant.

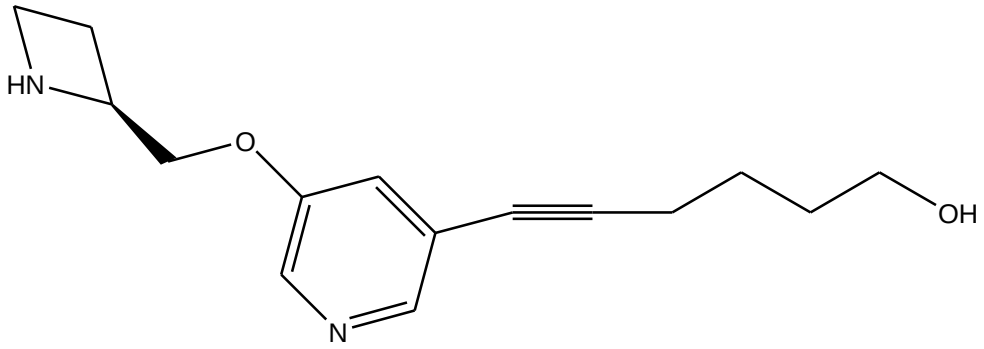
After subcutaneous and oral dosing, Andrés et al.[66] (2007) found that compound 2 (Fig. 1) was more powerful as a 5 HT reuptake inhibitor than as a 2 adrenoceptor blockers. Antidepressant development might be aided by targeting the 42 nicotinic receptors (nAChRs). By replacing Sazetidine-metabolically A's unstable acetylene with such a metabolically stability isoxazole ring,



(3*S*,3a*R*,*E*)-3-((4-(3-(4-fluorophenyl)-2-methylallyl)piperazin-1-yl)methyl)-7,8-dimethoxy-3a,4-dihydro-3*H*-chromeno[4,3-*c*]isoxazole

2

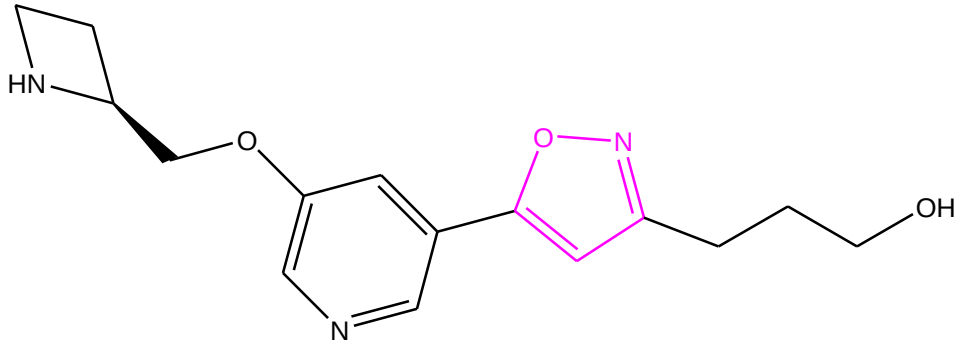
Liu et al.[67] (2011) synthesised numerous isoxazole analogues of Sazetidine-A (3; Fig. 1). Sazetidine A is a partial agonist that interacts with 42-nAChRs and has antidepressant properties.



(*R*)-6-(5-(azetidin-2-ylmethoxy)pyridin-3-yl)hex-5-yn-1-ol

3

The mouse forced-swim test revealed that compounda 4 (Fig. 1) had exceptional antidepressant behavioural activity. As partial agonist for 42 nAChRs, they are selective

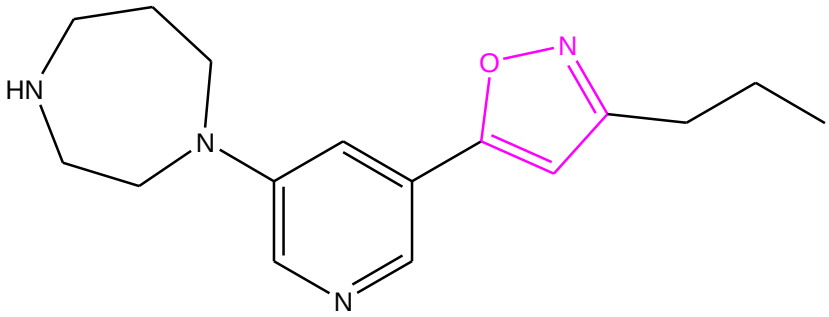


3-(5-(5-((*S*)-azetidin-2-ylmethoxy)pyridin-3-yl)isoxazol-3-yl)propan-1-ol

4

.

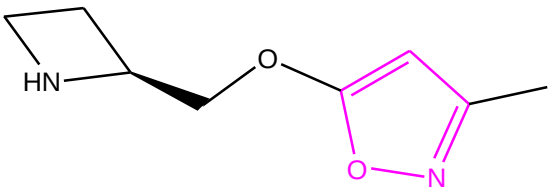
Zhang et al.[68] (2016) By combining substitution isoxazolyl functional groups with N-pyridyldiamines, a hybrid chemical was created. The force swim test revealed thatcompound 5 (Fig. 1) showed considerable antidepressant efficacy and great binding selectivity towards 42-nAChRs over 34-nAChRs. As nAChRs ligands,



1-(5-(3-propylisoxazol-5-yl)pyridin-3-yl)-1,4-diazepane

5

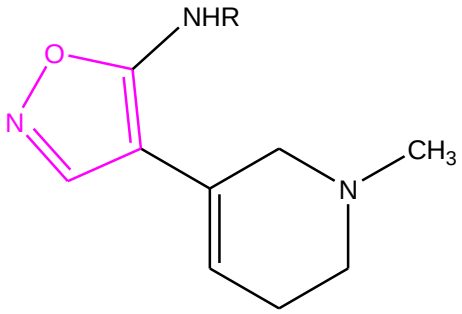
Yu et al.[69] (2012) developed a series of 5-alkoxy isoxazole. The majority of the compounds showed preference for rat 42 over 34-nAChRs. Compound 6 (Fig. 1) was the most selective of the bunch, with antidepressant-like effects.



(*S*)-5-(azetidin-2-ylmethoxy)-3-methylisoxazole

6

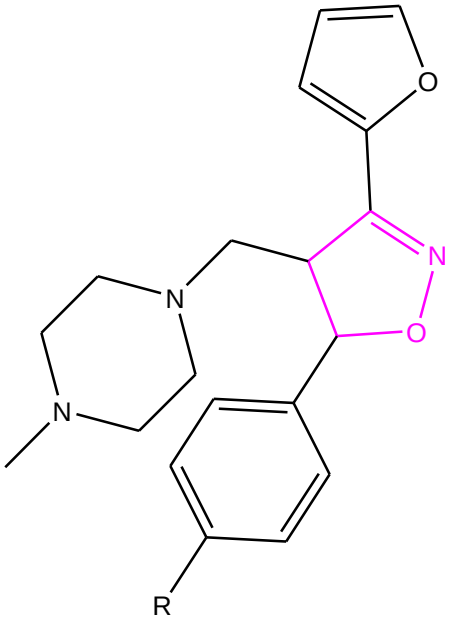
Olesen et al.[70] (1998) developed and tested a series of 3-((5-alkylamino- 4-isoxazolyl)-1,2,5,6-tetrahydropyridine (7; Figure. 1) for affinity & selectivity for central nicotinic receptors. Only monoalkyl amino-substituted drugs were discovered to have good affinity & selectivite for central nicotinic receptor. As the alkyl side group length grew up to propyl, the affinity increased. These chemicals have up to 10 fold greater affinity for the 42 receptors subtype than the 32 receptor sub-type when tested in cell line express the nicotinic receptors sub-types.



R= -H, Me, Et, Pr, Bu, C_6H_5

7

Kumar et al.[71] (2017) synthesised a series of 3,4,5-trisubstituted isoxazoles including the furan and piperazine moiety and tested them for antidepressant efficacy in albino mice using Porsolt's forced swimming test and antianxiety activity using the plus maze method.Compounds 8a and 8b (Fig. 1) were shown to have antidepressant and anti-anxiety properties.

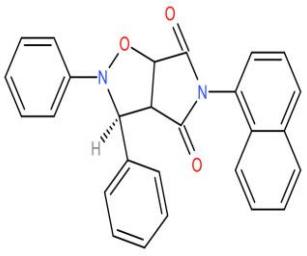


8a R= -H
8b R= -N(CH_3)$_2$ 8

These drugs have excellent binding interactions with MAO-A, according to molecular modelling studies .

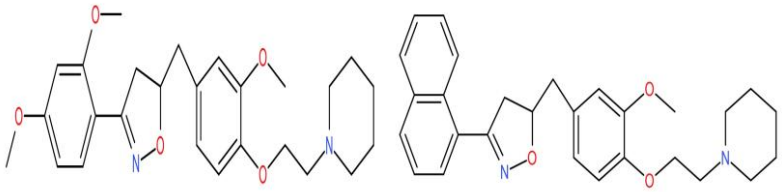
2.11. Antistress activity

Badru et al. [72] (2012) used a 1,3-dipolar cycloaddition of azomethine N oxides with N-(-naphthyl)maleimide to make a variety of pyrroloisoxazole derivatives. In immobilisation stress-induced increases in nonsocial behaviour, compound 1(Fig. 1) showed considerable anti-stress efficacy.



1

Maurya et al. [73] (2011) synthesised 3,5 disubstituted isoxazoline & assessed the anti stress potential in relation to peripheral and metabolic alterations under acute stress. Acute stress induced elevations Compounds 2 and 3 protected stomach ulceration patients against adrenal hypertrophy, hypoglycemia, plasma creatine kinase activities, & corticosterone levels. (Fig. 1).



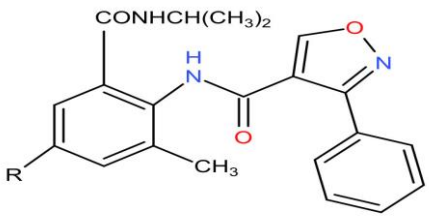
2 3

2.11.1. Mechanism of action of Anti-depressant activity

- Inhibition of serotonin reuptake into presynaptic cells, resulting in increased serotonin levels and increased post synaptic neuronal activity.
- They have no impact on nor epinephrine or dopamine.
- It usually takes 2 to 12 weeks for them to boost your mood..

2.12. Insecticidal activity

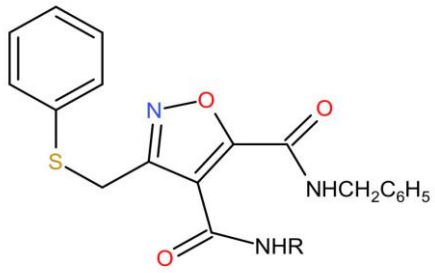
Peng-feiet al.[74] (2012) created several new phenyl substituted isoxazole carboxamides and tested them against Mythimna distinct (oriental armyworm). All compounds had moderate insecticidal action, with the exception of compounds 1a and 1b (Fig. 1), which had greater activity. Insecticidal action might be improved by combining aliphatic and aromatic amide moieties, according to SAR analyses.



1 a R=-H
b R=-Cl

Yu et al.[75] (2009) synthesised a sequence of 3-(arylthiomethyl)isoxazole-4,5-carboxamides (2; Fig. 1) and used high-throughput screening (HTS) to evaluate them for insecticidal activity against Spodoptera exigua (beet armyworm) and Aedes aegypti (yellow

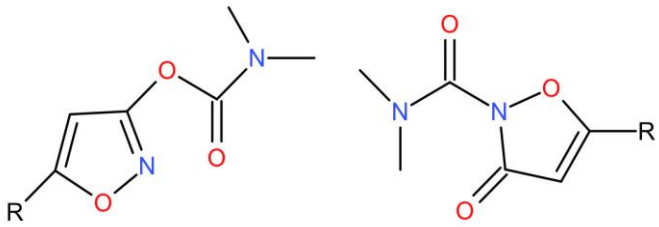
fever mosquito). According to the findings, 3,4,5-trisubstituted isoxazoles are a biological scaffold that might be exploited to develop novel insecticides.



R=-CH(CH$_3$)$_2$,-CH$_2$CH$_2$CH$_3$,-CH$_2$CH=CH$_2$

2

Verma et al. [76] (2015) investigated the AChE inhibitory and mosquitocidal properties of isoxazol-3-yl dimethylcarbamates (3; Fig. 1), as well as the corresponding 3-oxoisoxazole-2(3H)-dimethylcarboxamide isomers, ln attempt to identify mosquitocides that are both selective and resistant to the African malaria vector Anopheles gambiae (4; Fig. 1). Both series contained compounds with good contact toxicity to wild-type susceptible (G3) and multiply resistant (Akron) mosquitoes having the G119S AChE resistance mutation.



R=-Me,i-Pr,2-pentyl,3-pentyl,3-heptyl,neo-pentyl

3 **4**

Mechanism of action of Anti Insecticidalt activity

Most insecticides, such as organophosphorus and carbamate chemicals, have a toxicity mechanism based on acetylcholinesterase inhibition. Acetylcholinesterase (AChE) hydrolyzes the neurotransmitter acetylcholine (ACh) at the postsynaptic membrane to end neural excitation in insects.

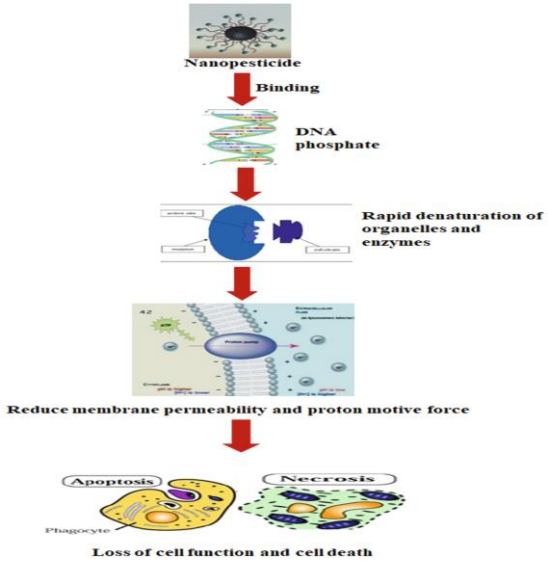
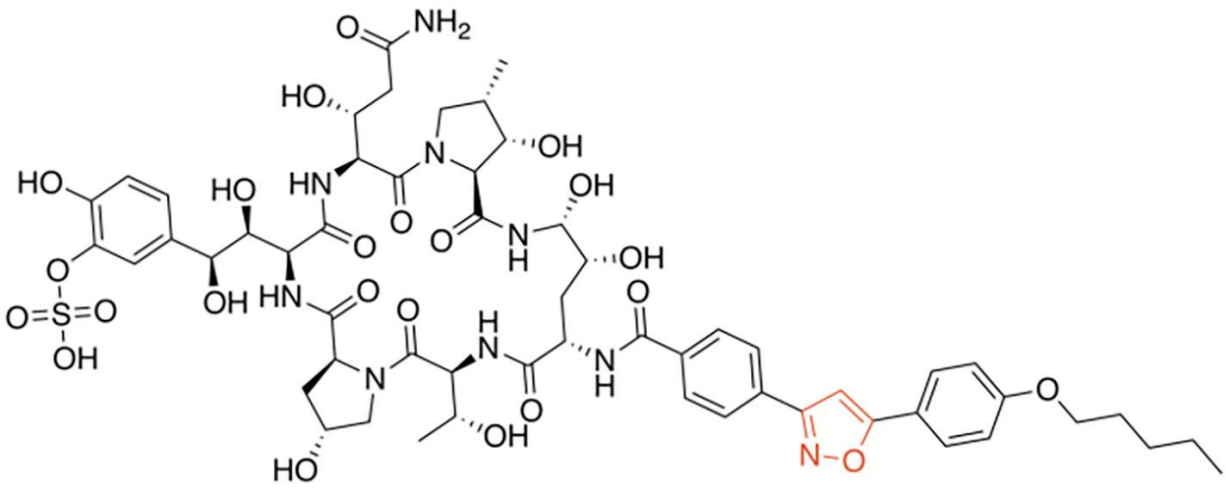


Figure 13 :Mechanism of action of Anti Insecticidalt activity

2.13. Antifungal agents

A fungicidal or fungistatic drug used to treat and prevent mycoses is known as an antifungal medicine. Invasive fungal infections are contagious and are linked to high rates of morbidity and death. [51]Fungi can also cause superficial infections (such as skin infections). A fungicidal or fungistatic drug used to treat and prevent mycoses is known as an antifungal medicine. [52] Even if it isn't life threatening. It has a considerable detrimental influence on the affected people' quality of life. Antifungal medicines containing an isoxazole ring on the market are uncommon. Other heterocyclic rings are referred to as heterocyclic ring. Micafungin is a kind of echinocandin, sometimes known as echinocandin. On March 16, 2005, the FDA approved an antifungal drug. Figure 1 It operates by inhibiting the production of 1,3-Beta-D-glucan, a key component of fungal cell walls. Micafungin's structure is shown in Figure 1. New broad-spectrum antifungal treatments are being developed in response to the growth in antifungal resistance & the unfavorable side effects of already available therapies. Antifungal drugs that are both safe and effective are urgently needed. Articles are published. The isoxazole moiety's antifungal activities are limited.



The structure of micafungin.

Santos et al. discovered 4 compound with promising antifungal properties activity at the g/mL level, ranging from a MIC-50 values of 0.2 g/mL to a MIC-50 values of 0.2g/mL PYCC-2545 (Candida parapsilosis) and PYCC-2418 T (Candida parapsilosis) glabrata) to 47.9g/mL against ATCC-90,028 (Candida glabrata). albicans). Compounds 1 & 2 (Figure. 2) displayed the largest spectrum. Amphotericin B, the typical antifungal medication, has superior action. Five of the six strains tested were found to be resistant. They also revealed no cytotoxicity.in human cellular lines, indicating that they have the potential to develop into Antifungal drugs with a broad scope and a low risk of side effects.[53]

Inspired by their pharmacological and biological qualities, Srinivas et al. combined thiazolidinone & isoxazole moieties in a one molecule. Antifungal activity was tested against Candida albicans (ATCC-10231), Aspergillus fumigatus (HIC-6094), Trichophyton rubrum (IFO-9185), & Trichophyton mentagrophytes (IFO-40996) using seven compounds. 3 & 4 were shown to have nearly equivalent activity against tested fungi as the conventional medicine Amphotericin B, and so identified as interesting molecules for further research.[54]

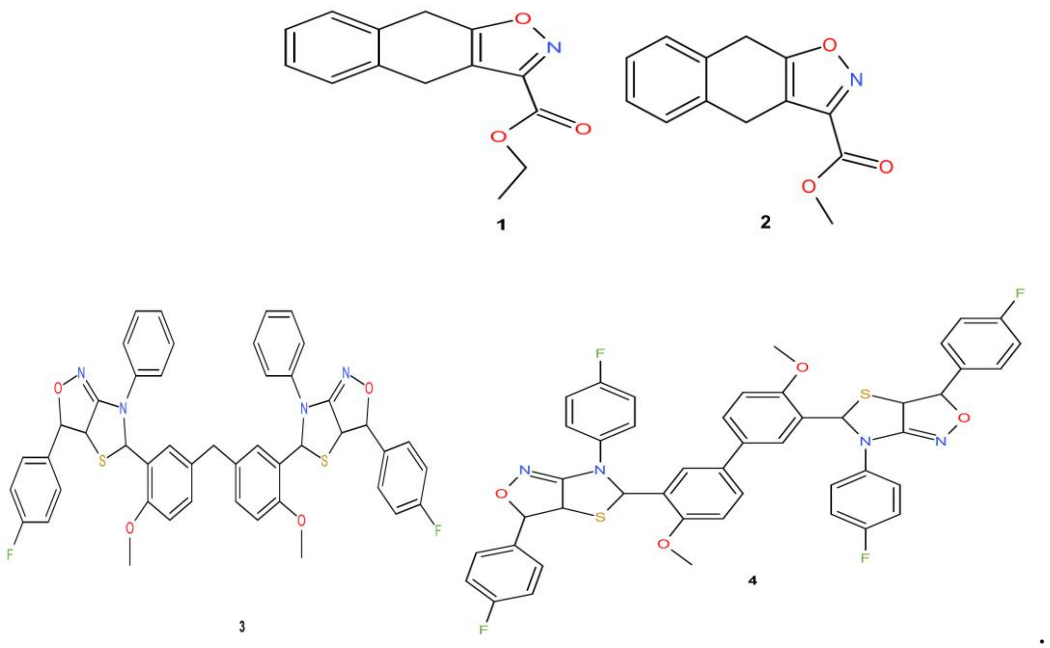


Figure 14 :Isoxazoles as antifungal agents

2.13.1. Mechanism of action of Antifungal agentstactivity

An alternate theory is that it works by inhibiting DNA synthesis. The imidazole derivatives stop fungus from making ergosterol, which is the major sterol in their membranes. Triglyceride and phospholipid production are also affected by these substances.

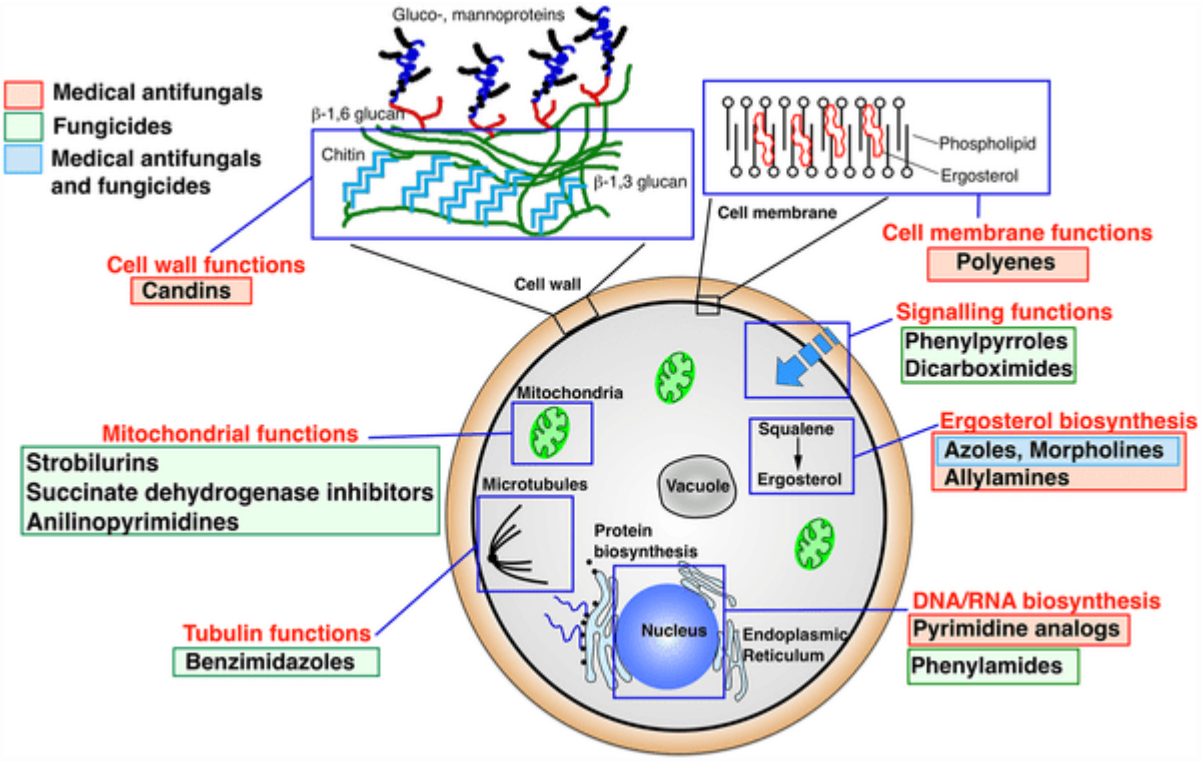
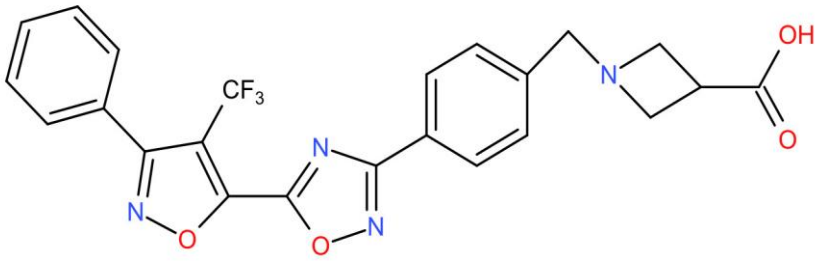


Figure 15 :Mechanism of action of Antifungal agentstactivity

2.14. Immunosuppressant activity

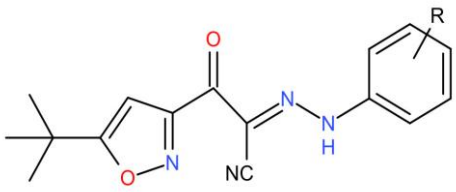
Antibodies against S1P1 have been found to inhibit lymphocyte trafficking from of the thymus and other lymphoid tissues, resulting in immunosuppressive.

Watterson et al. (2016) [81] synthesised a series of isoxazole synthesized from isoxazole-3-carboxylic acid & isoxazole-5-carboxylic acid to create selective S1P1 agonists Compound 1 (Figure. 1) emerged as a lead substance with excellent efficacy when supplied orally in a rat model of arthritic (ED50 0.05 mg/Kg) and a mice experiment autoimmunity encephalomyelitis version of multiple sclerosis (ED50-0.05mg/Kg). T-cell-mediated immunosuppression is one of the intracellular physiological functions in which EPACs play a role (Almahariq et al. 2015).[82]



1

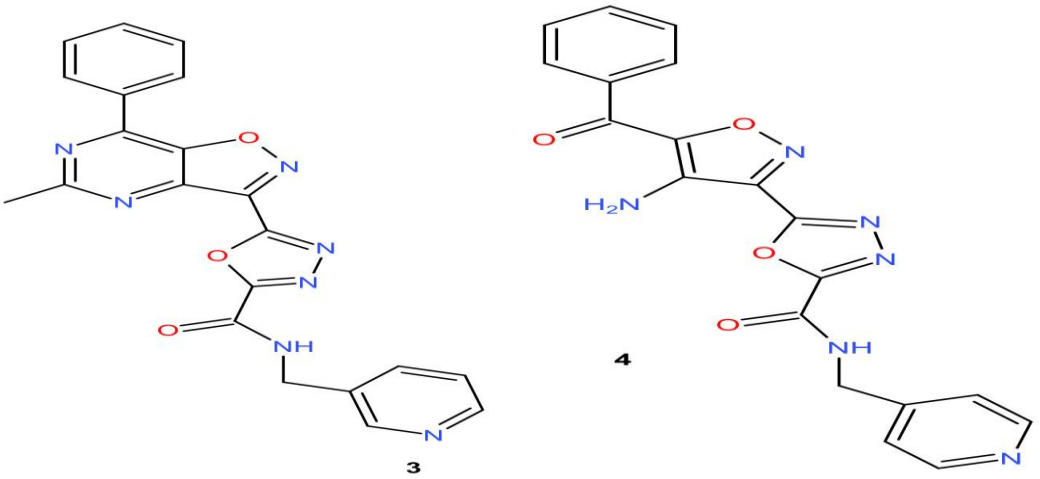
As EPAC antagonists, Ye et al. (2015) [83] developed a series of 2-(isoxazol-3-yl)-2-oxo-N'-phenyl-acetohydrazonoyl cyanide. Compounds 2a & 2b (Fig. 1) have been identified as possible inhibitors of EPAC-1 & EPAC-2. SAR analyses suggested that additional phenyl scaffold changes at the 3-, 4-, and 5-positions, as well as the 5-position of the isoxazole moiety, might result in more effective EPAC antagonists.



2 a R=3,5-di-Cl

b R=3,4-5-tri-Cl

In a mouse model, Wagner et al. (2008) [84] synthesisedisoxazolo[4,5-d]pyrimidine and evaluated its effects on immunological response. Compound 3 (Fig. 1) was discovered to be a general immune response inhibitor, whereas compound 4 (Fig. 1) reduced the humoral immune response specifically.



2.14.1.

Mechanism of action of Immunosuppressant activity

Immunosuppressive drugs, according to this theory, disrupt the immune system at various stages and levels. In a selective manner, glucocorticoids reduce the activity of monocytes and T-helper cells, as well as lymphokine production. Cyclosporin inhibits the production of interleukin-2 and has a specific effect on T cell function. All immune-system chevaliers' proliferative responses are reduced by azathioprine, cyclophosphamide, and methotrexate. The immunosuppressive characteristics of chloroquine are uncertain, however it appears to prevent the synthesis of thromboxane and interleukin-2. Antibodies against lymphoid element surface determinants are used to destroy whole populations of lymphoid elements. Antiidiotypic antibodies, which can be present in intravenous immunoglobulin preparations from a range of donors, work by binding to the idiotypic region of a disease-associated antibody to remove circulating (auto-)antibodies.

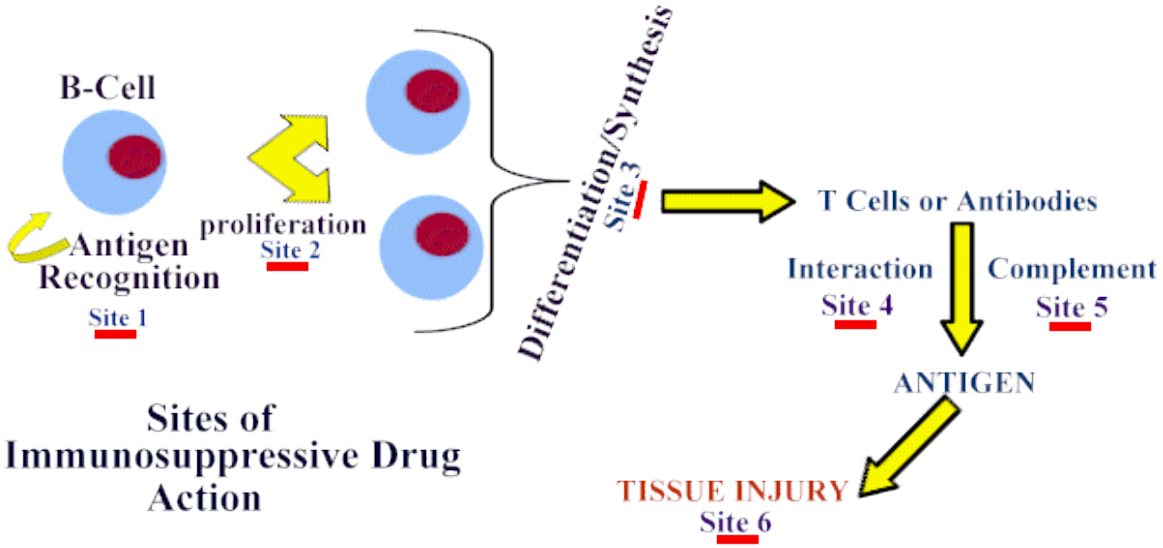
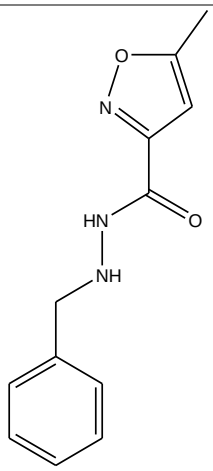
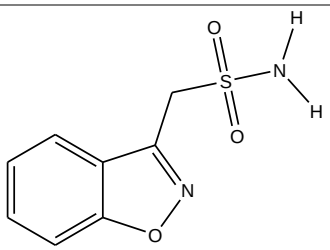
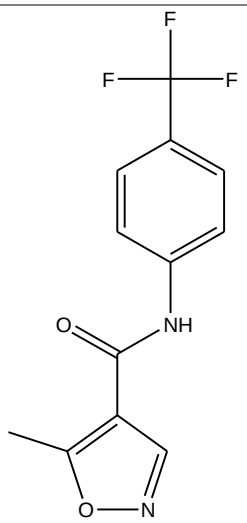
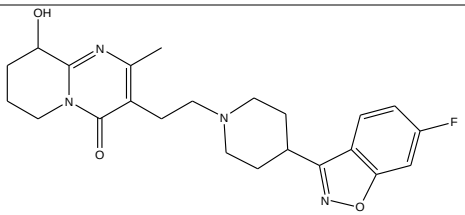
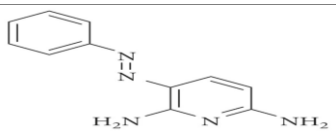
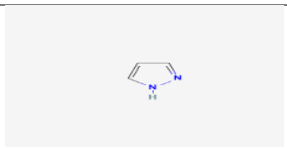
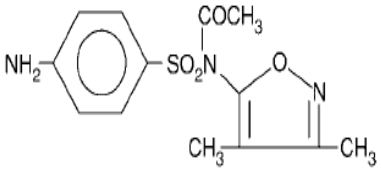


Figure 16 :Mechanism of action of Immunosuppressant activity

TABLE 1 :- NEW DRUG APPROVED BY FDA

S.NO.	DRUG NAME	STRUCTURE	CAS	APPROVAL DATE	REFERENCES
1	Isocarboxazid		59-63-2	08/18/1998	85
2	Zonisamide		68291-97-4	03/01/2000	86
3	Leflunomide		75706-12-6	09/10/1998	87
4	**SEROMYCIN**(Cycloserine)			06/29/1964	88

5	paliperidone			12/19/2006	89
6	**AZO GANTRISIN**		136-40-3	08/31/1990	90
7	**ERYZOLE**			06/15/1988	91
8	**GANTRISIN**			07/29/1948	92
9	**GANTRISIN PEDIATRIC**			12/04/1953	93
10	**PEDIAZOLE**			11/29/1979	94
11	**SOSOL**			02/09/1973	95
12	**SOXAZOLE**			06/07/1971	96
13	**SULFALAR**			01/05/1977	97
14	**SULFISOXAZOLE DIOLAMINE**			01/22/1975	98
15	**SULSOXIN**			06/15/1972	99

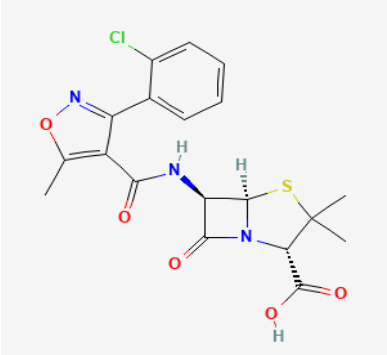
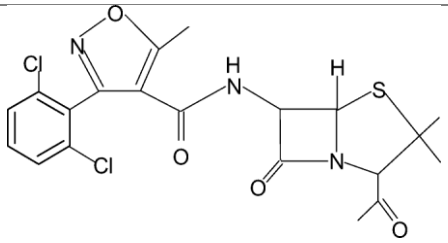
16	Cloxacillin		61-72-3	1965-August	101,102
17	Dicloxacillin		3116-76-5	1978-July	101’103

TABLE 2 :- NEW DRUGS APPROVED BY CDSCO

S.NO.	DRUG NAME	INDICATION	DATE OF APPROVAL	REF
1	Amoxycillin 250 mg + Dicloxacillin 250 mg cap	RTI,UTI, otitis media, dental abscess, septicaemia, soft tissue infection, & other bacterial illnesses caused by beta lactamase producing organisms.	28-08-2006	104
2	Cefixime 100mg + Cloxacillin (as Sodium) 500 mg + Lactobacillus (45 million spore)tab	Antibiotic	31-08-2006	104
3	Cefixime 200mg + Cloxacillin 500mg (ER) + Lactobacillus 90 million Spore tab. (additional strength)	Antibiotic	14-11-2006	104
4	Ampicillin 250mg + Dicloxacillin 250mg tablet	Antibiotic	13-12-2006	104
5	Cefixime 200 mg + Dicloxacillin ER 500mg Tablets	Adults with upper & lower respiratory tract infections, as well as skin & soft tissue infection, are treated with this medication.	22-09-2009	104
6	Cefpodoxime 100/200mg + Dicloxacillin ER 500/500mg	Treatment of lower RI, skin & soft tissue infections, bone & joint	06-08-2010	104

		infection, & ENT infections in people who are susceptible to antibiotic-induced diarrhoea..		
7	Cefixime 100 mg / 200 mg + Cloxacillin 500mg / 500mg tablets.	For the treatment of upper & lower respiratory tract infection, as well as skin & soft tissue diseases in adults.	12-02-10	104
8	Leflunomide [10mg/20mg/100mg]	"Active psoriatic arthritis i**n** adults only" as an extra indication, subject to the conditions of 4-136/04 dt. 30-08-2004.	29-11-2004	104
9	Leflunomide film coated tablets	Active psoriatic arthritis in adults is an additional indication.	30/08/2004	104
10	Leflunomide tab	Only for people with active rheumatoid arthritis.	01/10/2001	104

CONCLUSION

This study paper provides a literature-based overview of isoxazole derivatives, focusing on their biological activity, prospective therapeutic applications, and chemical structure. Antimicrobial, antiviral, anticancer, immunomodulatory, anti-inflammatory, analgesic, & anti-diabetic characteristics are among the most commonly characterised isoxazole properties. It can be inferred that the activity of these compound is determined by their structure, & that the inclusion of electronegative substituent increased their potency in the majority of situations. These findings might be useful in the creation of isoxazole derivatives for the delivery of novel medicinal medicines.

REFERENCES

[1] **https://doi.org/10.1002/adsc.201500319**

[2]https://pubmed.ncbi.nlm.nih.gov/34000484

[3] A. Barmade M, R. Murumkar P, Kumar Sharma M, Ram Yadav M. 2016. Medicinal Chemistry Perspective of Fused Isoxazole Derivatives. Curr Top Med Chem [Internet]. [cited 2021 Dec 4]; 16:2863–2883. Available from: https://pubmed.ncbi.nlm.nih.gov/27150366

[4]Abu-Hashem AA, El-Shazly M. 2018. Synthesis of New Isoxazole-, Pyridazine-, Pyrimidopyrazines and Their Anti-Inflammatory and Analgesic Activity. Med Chem [Internet]. [cited 2021 Dec 4]; 14. Available from: https://pubmed.ncbi.nlm.nih.gov/29332598/

[5]Algethami FK, Cherif M, Jlizi S, Hamadi N Ben, Romdhane A, Elamin MR, Alghamdi MA, Jannet H Ben. 2021. Design, microwave-assisted synthesis and in silico prediction study of novel isoxazole linked pyranopyrimidinone conjugates as new targets for searching potential anti-SARS-CoV-2 agents. Molecules [Internet]. [cited 2021 Dec 5]; 26. Available from:https://pubmed.ncbi.nlm.nih.gov/34684683

[6]Ali MA, Ismail R, Choon TS, Pandian S, Hassan Ansari MZ. 2011. Antimycobacterial activity: Synthesis of novel 3-(substituted phenyl)-6,7-dimethoxy-3a,4-dihydro-3H-indeno[1,2-c]isoxazole analogues. J Enzyme Inhib Med Chem. 26:598–602.

[7]Beyzaei H, Kamali Deljoo M, Aryan R, Ghasemi B, Zahedi MM, Moghaddam-Manesh M. 2018. Green multicomponent synthesis, antimicrobial and antioxidant evaluation of novel 5-amino-isoxazole-4-carbonitriles. Chem Cent J [Internet]. [cited 2021 Dec 4]; 12:1–8. Available from: https://bmcchem.biomedcentral.com/articles/10.1186/s13065-018-0488-0

[8]Bormann A. 2009. Review of the pharmacology and clinical studies of micafungin. Drug Des Devel Ther [Internet]. [cited 2021 Dec 4]; 3:295. Available from:

https://pubmed.ncbi.nlm.nih.gov/20054447/

[9]Chawla C, Indoriya S, Jain R, Sharma S. 2014. A highly efficient, Simple and ecofriendly microwave-induced synthesis of indolyl chalcones and isoxazoles. J Chem Pharm Res [Internet]. [cited 2021 Dec 5]; 6:2097–2104. Available from:www.jocpr.com

[10]CHIKKULA KV, RAJA S. 2017. ISOXAZOLE–A POTENT PHARMACOPHORE. Int J Pharm Pharm Sci [Internet]. [cited 2021 Dec 9:13 24.Availablefrom:https://innovareacademics.in/journals/index.php/ijpps/article/view/19097/11555

[11]. Hamama WS, Ibrahim ME, Zoorob HH. Synthesis and Biological Evaluation of Some Novel Isoxazole Derivatives. J Heterocycl Chem. 2017;54:341–6. doi:10.1002/jhet.2589.

[12]. Ghorab MM, Bashandy MS, Alsaid MS. Novel thiophene derivatives with sulfonamide, isoxazole, benzothiazole, quinoline and anthracene moieties as potential anticancer agents. Acta Pharm. 2014;64:419–31. doi:10.2478/ACPH-2014-0035.

[13]. Kalirajan R, Rafick MHM, Sankar S, Jubie S. Docking studies, synthesis, characterization and evaluation of their antioxidant and cytotoxic activities of some novel isoxazole-substituted 9-anilinoacridine derivatives. Sci World J. 2012;2012. doi:10.1100/2012/165258.

[14]. Rollas S. Synthesis and evaluation of cytotoxic activities of some substituted isoxazolone derivatives. MARMARA Pharm J. 2011;3:94–9. doi:10.12991/201115424.

[15]. Li X, Zhang J, Zhao L, Yang Y, Zhang H, Zhou J. Design, Synthesis, and in vitro Biological Evaluation of 3,5-Dimethylisoxazole Derivatives as BRD4 Inhibitors. ChemMedChem. 2018;13:1363–8. doi:10.1002/CMDC.201800074.

[16]. Yong J-P, Lu C-Z, Wu X. Potential anticancer agents. I. Synthesis of isoxazole moiety containing quinazoline derivatives and preliminarily in vitro anticancer activity. Anticancer Agents Med Chem. 2015;15:131–6. doi:10.2174/1871520614666140812105445.

[17]. Vekariya NA, Khunt MD, Parikh AR. Synthesis of isoxazoles and quinoxalines as potential anticancer agents. Indian J Chem - Sect B Org Med Chem. 2003;42:421–4. doi:10.1002/CHIN.200322165.

[18]. Rajanarendar E, Rama Krishna S, Nagaraju D, Govardhan Reddy K, Kishore B, Reddy YN (2015) Environmentally benig synthesis, molecular properties prediction and anti-inflammatory activity of novel isoxazolo[5,4-d]isoxazol-3-yl-aryl-methanones via vinylogous Henry nitroaldol adducts as synthons. Bioorg Med Chem Lett 25:1630–1634.

[19]. Panda S, Chowdary P, Jayashree B (2009) Synthesis, anti-inflammatory and antibacterial activity of novel indolyl-isoxazoles. Indian J Pharm Sci 71:684–687.

[20]. Amir M, Javed SA, Kumar H (2010) Design and synthesis of 3-[3-(substituted phenyl)-4-piperidin-1-ylmethyl/-4-morpholin-4-ylmethyl-4,5-dihydro-isoxazol-5-yl]-1H-indoles as potent antiinflammatory
agents. Med Chem Res 19:299–310.

[21]. Karthikeyan K, Veenus Seelan T, Lalitha KG, Perumal PT (2009) Synthesis and antinociceptive activity of pyrazolyl isoxazolines and pyrazolyl isoxazoles. Bioorg Med Chem Lett 19:3370–3373.

[22].Ostacolo C, Ambrosino P, Russo R, Lo Monte M, Soldovieri MV, Laneri S, Sacchi A, Vistoli G, Taglialatela M, Calignano A (2013) Isoxazole derivatives as potent transient receptor potential melastatin type 8 (TRPM8) agonists. Eur J Med Chem 69:659–669.

[23]. Palin R, Abernethy L, Ansari N, Cameron K, Clarkson T, Dempster M, Dunn D, Easson AM, Edwards D, MacLean J, Everett K, Feilden H, Ho KK, Kultgen S, Littlewood P, McArthur D,McGregor D, McLuskey H, Neagu I, Neale S, Nisbet LA, Ohlmeyer M, Pham Q, Ratcliffe P, Rong Y, Roughton A, Sammons M, Swanson R, Tracey H, Walker G (2011) Structure-activity studies of a novel series of isoxazole-3-carboxamide derivatives as TRPV1 antagonists. Bioorg Med Chem Lett 21:892–898.

[24]. Banoglu E, Çelikoglu E, Volker S, Olgac A, Gerstmeier J, Garscha U, Caliskan B, Schubert US, Carotti A, Macchiarulo A, Werz O (2016) 4,5-Diarylisoxazol-3-carboxylic acids: A new class of leukotriene biosynthesis inhibitors potentially targeting 5-lipoxygenaseactivating protein (FLAP). Eur J Med Chem 113:1–10.

[25]. Silva NM, Tributino JLM, Miranda ALP, Barreiro EJ, Fraga CAM (2002) New isoxazole derivatives designed as nicotinic acetylcholine receptor ligand candidates. Eur J Med Chem 37:163–170.

[26].Peifer C, Abadleh M, Bischof J, Hauser D, Schattel V, Hirner H, Knippschild U, Laufer S (2009) 3,4-Diaryl-isoxazoles and –imidazoles as potent dual inhibitors of p38α mitogen activated protein kinase and casein kinase 1δ. J Med Chem 52:7618–7630.

[27]. Peifer C, Wagner G, Laufer S (2006) New approaches to the treatment of inflammatory disorders small molecule inhibitors of p38 MAP kinase. Curr Top Med Chem 6:113–149

[28]. Laufer SA, Margutti S, Fritz MD (2006) Substituted isoxazoles as potent inhibitors of p38 MAP kinase. ChemMedChem 1:197–207.

[29]. RamaRao RJ, Rao AKSB, Sreenivas N, Kumar BS, Murthy YLN (2011) Synthesis and antibacterial activity of novel 5-(heteroaryl) isoxazole Derivatives. J Korean Chem Soc 55:243–250.

[30]. Gautam KC, Singh DP (2013) Synthesis and antimicrobial activity of some isoxazole derivatives of thiophene. Chem Sci Trans 2:992–996.

[31]. Basha SS, Divya K, Padmaja A, Padmavathi V (2015) Synthesis and antimicrobial activity of thiazolyl pyrazoles and isoxazoles. ResChemIntermed 41:10067–10083.

[32]. Lavanya G, Mallikarjuna Reddy L, Padmavathi V, Padmaja A (2014) Synthesis andantimicrobial activity of (1,4-phenylene)bis(arylsulfonylpyrazoles and isoxazoles). Eur J Med Chem 73:187–194.

[33Zhao S, Zhang X, Wei P, Su X, Zhao L, Wu M, Hao C, Liu C, Zhao D, Cheng M (2017b) Design, synthesis and evaluation of aro-matic heterocyclic derivatives as potent antifungal agents. EurJMed Chem 137:96–107

[34]. Agirbas H, Guner S, Budak F, Keceli S, Kandemirli F, Shvets N, Kovalishyn V, Dimoglo A (2007) Synthesis and structure–antibacterial activity relationship investigation of isomeric 2,3,5-substituted perhydropyrrolo[3,4-d]isoxazole-4,6- diones. Bioorg Med Chem 15:2322–2333.

[35]. Sahu S, Banerjee M, Sahu D, Behera C, Pradhan G, Azam MA (2009) Synthesis, analgesic and antimicrobial activities of some novel isoxazole derivatives. Daka Univ J Pharm Sci 7:113–118.

[36] N. Jaradat, M. Qneibi, M. Hawash et al., "Chemical composition, antioxidant, antiobesity, and antidiabetic effects of Helichrysum sanguineum (L.) Kostel. From Palestine," Arabian Journal for Science and Engineering, vol. 46, no. 1, pp. 41–51, 2021.View at: Publisher Site | Google Scholar

[37] A. Bouyahya, N. El Moussaoui, J. Abrini, Y. Bakri, and N. Dakka, "In vitro Antibacterial Activity of Organic extracts from North-West Moroccan Medicinal Plant Myrtus communis (L.)," Biotechnology Journal International, vol. 16, no. 4, pp. 1–9, 2016.View at: Publisher Site | Google Scholar

[38] Eugenio, J.G.; Tatiane, L.C.O.; Severino, M.A.; Alessandra, R.; Alessandro, D.L.; Rosa, H.M.G. Antioxidant activity by DPPH assay of potential solutions to be applied on bleached teeth. Braz. Dent. J. 2012, 23, 22–27

[39] Y.S. Lee, B.H. Kim, Heterocyclic nucleoside analogues: Design and synthesis ofantiviral, modified nucleosides containing isoxazole heterocycles, Bioorganic & MedicinalChemistry Letters, 12 (2002) 1395-1397.

[40] S. Srivastava, L.K. Bajpai, S. Batra, A.P. Bhaduri, J.P. Maikhuri, G. Gupta, J.D. Dhar, In search of new chemical entities with spermicidal and anti-HIV activities, Bioorganic &Medicinal Chemistry, 7 (1999) 2607-2613.

[41] V.A. Makarov, O.B. Riabova, V.G. Granik, P. Wutzler, M. Schmidtke, Novel(biphenyloxy)propyl isoxazole derivatives for inhibition of human rhinovirus 2 andcoxsackievirus B3 replication, Journal of Antimicrobial Chemotherapy, 55 (2005) 483-488.

[42] B.L. Deng, Y.J. Zhao, T.L. Hartman, K. Watson, R.W. Buckheit, C. Pannecouque, E. De Clercq, M. Cushman, Synthesis of alkenyldiarylmethanes (ADAMs) containing benzo disoxazole and oxazolidin-2-one rings, a new series of potent non-nucleoside HIV-1 reverse transcriptase inhibitors, European Journal of Medicinal Chemistry, 44 (2009) 1210-1214.

[43] T. Liu, B.S. Huang, P. Zhan, E. De Clercq, X.Y. Liu, Discovery of small molecularinhibitors targeting HIV-1 gp120-CD4 interaction drived from BMS-378806, EuropeanJournal of Medicinal Chemistry, 86 (2014) 481-490.

[44] F. Li, C.L. Ma, W.F. DeGrado, J. Wang, Discovery of Highly Potent Inhibitors Targeting the Predominant Drug-Resistant S31N Mutant of the Influenza A Virus M2 Proton Channel,Journal of Medicinal Chemistry, 59 (2016) 1207-1216.

[45] F. Li, Y.M. Hu, Y.X. Wang, C.L. Ma, J. Wang, Expeditious Lead Optimization ofIsoxazole-Containing Influenza A Virus M2-S31N Inhibitors Using the Suzuki-MiyauraCross-Coupling Reaction, Journal of Medicinal Chemistry, 60 (2017) 1580-1590.

[46] S. Batra, T. Srinivasan, S.K. Rastogi, B. Kundu, A. Patra, A.P. Bhaduri, M. Dixit,Combinatorial synthesis and biological evaluation of isoxazole-based libraries as antithrombotic agents, Bioorganic & Medicinal Chemistry Letters, 12 (2002) 1905-1908.

[47] C.B. Xue, J. Roderick, S. Mousa, R.E. Olson, W.F. DeGrado, Synthesis and antiplatelet effects of an isoxazole series of glycoprotein IIb/IIIa antagonists, Bioorganic & Medicinal Chemistry Letters, 8 (1998) 3499-3504

.

[48] R.D. Jadhav, K.S. Kadam, S. Kandre, T. Guha, M.M.K. Reddy, M.K. Brahma, N.J.Deshmukh, A. Dixit, L. Doshi, N. Potdar, A.A. Enose, R.A. Vishwakarma, H. Sivaramakrishnan, S. Srinivasan, K.V.S. Nemmani, A. Gupte, A.K. Gangopadhyay,

R.Sharma, Synthesis and biological evaluation of isoxazole, oxazole, and oxadiazole containing heteroaryl analogs of biarylureas as DGAT1 inhibitors, European Journal of Medicinal Chemistry, 54 (2012) 324-342.

[49] P. Vitale, S. Tacconelli, M.G. Perrone, P. Malerba, L. Simone, A. Scilimati, A.Lavecchia, M. Dovizio, E. Marcantoni, A. Bruno, P. Patrignani,Synthesis,Pharmacological Characterization, and Docking Analysis of a Novel Family of Diarylisoxazoles as Highly Selective Cyclooxygenase-1 (COX-1) Inhibitors, Journal of Medicinal Chemistry, 56 (2013) 4277-4299.

[50] H.Y. Zhao, G. Liu, Z.L. Xin, M.D. Serby, Z.H. Pei, B.G. Szczepankiewicz, P.J. Hajduk,C. Abad-Zapatero, C.W. Hutchins, T.H. Lubben, S.J. Ballaron, D.L. Haasch, W. Kaszubska,C.M. Rondinone, J.M. Trevillyan, M.R. Jirousek, Isoxazole carboxylic acids as protein tyrosine phosphatase 1B (PTP1B) inhibitors, Bioorganic & Medicinal Chemistry Letters, 14 (2004) 5543-5546.

[51] J.Y. Bass, R.D. Caldwell, J.A. Caravella, L.H. Chen, K.L. Creech, D.N. Deaton, K.P.Madauss, H.B. Marr, R.B. McFadyen, A.B. Miller, D.J. Parks, D. Todd, S.P. Williams, G.B.Wisely, Substituted isoxazole analogs of farnesoid X receptor (FXR) agonist GW4064,Bioorganic & Medicinal Chemistry Letters, 19 (2009) 2969-2973.

[52] L.Y. Yang, J. Zhang, L.H. Si, L. Han, B. Zhang, H. Ma, J.H. Xing, L.L. Zhao, J.P. Zhou,H.B. Zhang, Synthesis and biological evaluation of GPR40/FFAR1 agonists containing 3,5-dimethylisoxazole, European Journal of Medicinal Chemistry, 116 (2016) 46-58.

[53] M.A. Kalwat, Z.M. Huang, C. Wichaidit, K. McGlynn, S. Earnest, C. Savoia, E.M.Dioum, J.W. Schneider, M.R. Hutchison, M.H. Cobb, Isoxazole Alters Metabolites and Gene Expression, Decreasing Proliferation and Promoting a Neuroendocrine Phenotype in beta-Cells, Acs Chemical Biology, 11 (2016) 1128-1136.

[54] R. Narlawar, M. Pickhardt, S. Leuchtenberger, K. Baumann, S. Krause, T. Dyrks, S.Weggen, E. Mandelkow, B. Schmidt, Curcumin-derived pyrazoles and isoxazoles:

Swissarmy knives or blunt tools' for Alzheimer's disease?,Chemmedchem, 3 (2008) 165-172.

[55] S.M. Lenz, E. Meier, H. Pedersen, K. Frederiksen, K.P. Bogeso, P. Krogsgaardlarsen,Muscarinic agonists- syntheses and structure-activity relationships of bicyclic isoxazole ester bioisosteres of norarecoline, European Journal of Medicinal Chemistry, 30 (1995) 263-270.

[56] Kachhadia VV, Patel MR, Joshi HS (2004) Synthesis of isoxazoles and cyanopyridines bearing benzo (b) thiophene nucleus aspotential antitubercular and antimicrobial agents. J Sci IslamRepub Iran 15:47–51

[57] Patel D, Kumari P, Patel NB (2014) Synthesis and biological evaluation of coumarin based isoxazoles, pyrimidinthiones andpyrimidin-2-ones. Arab J Chem 10:S3990–S4001

[58] Changtam C, Hongmanee P, Suksamrarn A (2010) Isoxazole analogs of curcuminoids with highly potent multidrug-resistant antimycobacterial activity. Eur J Med Chem 45:4446–4457

[59] Joshi SD, Dixit SR, Kirankumar MN, Aminabhavi TM, Raju KVSN, Narayan R, Lherbet C, Yang KS (2016) Synthesis, antimycobacterialscreening and ligand-based molecular dockingstudies on novel pyrrole derivatives bearing pyrazoline, isoxazoleand phenyl thiourea moieties. Eur J Med Chem 107:133–152

[60] Naidu KM, Suresh A, Subbalakshmi J, Sriram D, Yogeeswari P, Raghavaiah P, Chandra Sekhar KVG (2014) Design, synthesisand antimycobacterial activity of various 3-(4-(substituted sulfonyl)piperazin-1-yl)benzo[d]isoxazole derivatives. Eur J MedChem 87:71–78

[61] Mao J, Yuan H, Wang Y, Wan B, Pak D, He R, Franzblau SG (2010) Synthesis and antituberculosis activity of novel mefloquineisoxazole carboxylic esters as prodrugs. Bioorg Med Chem Lett20:1263–1268

[62] Yamuna E, Kumar RA, Zeller M, Rajendra Prasad KJ (2012) Synthesis, antimicrobial, antimycobacterial and structure-activity relationshipof substituted pyrazolo-, isoxazolo-, pyrimido- andmercaptopyrimidocyclohepta[b]indoles. Eur J Med Chem47:228–238

[63] Rakesh SD, Lee RB, Tangallapally RP, Lee RE (2009) Synthesis, optimization and structure-activity relationships of 3,5-disubstituted isoxazolines as new anti-tuberculosis agents. EurJMed Chem 44:460–472

[64] Patil PO, Bari SB (2013) Synthesis and Antidepressant activity of some new 5-(1H-indol-3-yl)-3-(substituted aryl)-4,5-dihydroisoxazoline derivatives. J Chem 2013:1–8

[65] Andrés JI, Alcázar J, Alonso JM, Alvarez RM, Cid JM, De Lucas AI, Fernández J, Martıń ez S, Nieto C, Pastor J, Bakker MH, BiesmansI, Heylen LI, Megens AA (2003) Synthesis of 3a,4-dihydro-3H-[1]benzopyrano[4,3-c]isoxazoles, displaying combined 5-HTuptake inhibiting and α2-adrenoceptor antagonistic activities: anovel series of potential antidepressants. Bioorg Med Chem Lett13:2719–2725

[66] Andrés JI, Alcázar J, Alonso JM, Alvarez RM, Bakker MH, Biesmans I, Cid JM, De Lucas AI, Drinkenburg W, Fernández J, Font LM, Iturrino L, Langlois X, Lenaerts I, Martıń ez S, MegensAA,Pastor J, Pullan S, Steckler T (2007) Tricyclic isoxazolines:Identification of R226161 as a potential new antidepressant thatcombines potent serotonin reuptake inhibition and α2-adrenoceptorantagonism. Bioorg Med Chem 15:3649–3660

[67] Liu J, Yu LF, Eaton JB, Caldarone B, Cavino K, Ruiz C, Terry M,Fedolak A, Wang D, Ghavami A, Lowe DA, Brunner D, LukasRJ, Kozikowski AP (2011) Discovery of isoxazole analogues ofsazetidine-A as selective α4β2-nicotinic acetylcholine receptorpartial agonists for the treatment of depression. J Med Chem54:7280–7288

[68] Zhang HK, Eaton JB, Fedolak A, Gunosewoyo H, OnajoleOK,Brunner D, Lukas RJ, Yu LF, Kozikowski AP (2016) Synthesisand biological evaluation of novel hybrids of highly potent andselective α4β2-Nicotinic acetylcholine receptor (nAChR) partialagonists. Eur J Med Chem 124:689–697

[69] Yu L-F, Tückmantel W, Eaton JB, Caldarone B, Fedolak A, Hanania T, Brunner D, Lukas RJ, Kozikowski AP (2012) Identification ofnovel α4β2-nicotinic acetylcholine receptor (nAChR) agonistsbased on an isoxazole ether scaffold that demonstrateantidepressant-like activity. J Med Chem 55:812–823

[70] Olesen PH, Swedberg MDB, Rimvall K (1998) 3-(5-Alkylamino-4-isoxazolyl)-1,2,5,6-tetrahydropyridines: a novel class of centralnicotinic receptor ligands. Bioorg Med Chem 6:1623–1629

[71] Kumar J, Chawla G, Akhtar M, Sahu K, Rathore V, Sahu S (2017) Design, synthesis and pharmacological evaluation of some novelderivatives of 1-{[3-(furan-2-yl)-5-phenyl-4,5-dihydro-1,2-oxazol-4-yl]methyl}-4-methyl piperazine. Arab J Chem 10:141–149

[72] Badru R, Anand P, Singh B (2012) Synthesis and evaluation of hexahydropyrrolo[3,4-d]isoxazole-4,6-diones as anti-stress agents.Eur J Med Chem 48:81–91

[73] Maurya R, Ahmad A, Gupta P, Chand K, Kumar M, Jayendra, Rawat P, Rasheed N, Palit G (2011) Synthesis of novel isoxazolines via1,3-dipolar cycloaddition and evaluation of anti-stress activity.Med Chem Res 20:139–145

[74] Peng-fei L, Ji-feng Z, Tao Y, Li-xia X, Zheng-ming LI (2012) Design, synthesis and insecticidal activities of novel phenyl substitutedisoxazolecarboxamides. Chem Res Chin Univ 28:430–433

[75] Yu GJ, Iwamoto S, Robins LI, Fettinger JC, Sparks TC, Lorsbach BA, Kurth MJ (2009) 3-(Arylthiomethyl)isoxazole-4,5-dicarboxamides:chemoselective nucleophilic chemistry and insecticidalactivity. J Agric Food Chem 57:7422–7426

[76] Verma A, Wong DM, Islam R, Tong F, Ghavami M, Mutunga JM,Slebodnick C, Li J, Viayna E, Lam PC-H, Totrov MM, BloomquistJR, Carlier PR (2015) 3-Oxoisoxazole-2(3H)-carboxamides and isoxazol-3-yl carbamates: Resistance-breaking acetylcholinesteraseinhibitors targeting the malaria mosquito, Anophelesgambiae. Bioorg Med Chem 23:1321–1340

[77] Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers:human fungal infections. Sci Transl Med. 2012;4(165):165rv13.

[78] Kumar L, Verma S, Bhardwaj A, Vaidya S, Vaidya B. Eradication of superficialfungal infections by conventional and novel approaches: a comprehensive review.Artif Cells NanomedBiotechnol. 2014;42:32–46.

[79] Santos MMM, Faria N, Iley J, et al. Reaction of naphthoquinones with substitutednitromethanes. Facile synthesis and antifungal activity of naphtho[2,3-d] isoxazole-4,9-diones. Bioorg Med Chem Lett. 2010;20:193–195.

[80] Srinivas A, Nagaraj A, Reddy CS. Synthesis and in vitro study of methylene-bistetrahydro[1,3] thiazolo [4,5-c]isoxazoles as potential nematicidal agents. EurJMed Chem. 2010;45:2353–2358

[81] Watterson SH, Guo J, Spergel SH, Langevine CM, Moquin RV, ShenDR, Yarde M, Cvijic ME, Banas D, Liu R, Suchard SJ, GilloolyK, Taylor T, Rex-Rabe S, Shuster DJ, McIntyre KW, CorneliusG, D'Arienzo C, Marino A, Balimane P, Warrack B, Salter-CidL, McKinnon M, Barrish JC, Carter PH, Pitts WJ, Xie J, DyckmanAJ (2016) Potent and selective agonists of sphingosine 1-phosphate 1 (S1P1): Discovery and SAR of a novel isoxazolebased series. J Med Chem 59:2820–2840

[82] Almahariq M, Mei FC, Wang H, Cao AT, Yao S, Soong L, Sun J,Cong Y, Chen J, Cheng X (2015) Exchange protein directlyactivated by cAMP modulates regulatory T-cell-mediatedimmunosuppression. Biochem J 465:295–303

[83] Ye N, Zhu Y, Chen H, Liu Z, Mei FC, Wild C, Chen H, Cheng X, Zhou J (2015) Structure-activity relationship studies of substituted 2-(isoxazol-3-yl)-2-oxo-N'-phenyl-acetohydrazonoylcyanide analogues: identification of potent exchange proteinsdirectly activated by cAMP (EPAC) antagonists. J Med Chem58:6033–6047

[84] Wagner E, Al-Kadasi K, Zimecki M, Sawka-Dobrowolska W (2008) Synthesis and pharmacological screening of derivatives of isoxazolo[4,5-d]pyrimidine. Eur J Med Chem 43:2498–2504.

[85] https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/11961-s017.cfm#:~:text=Approval%20Date%3A%208%2F18%2F1998

[86] https://www.accessdata.fda.gov/drugsatfdadocs/nda/2000/020789_Zonegran.cfm#:~:text=Approval%20Date%3A%203%2F1%2F2000

[87] https://www.accessdata.fda.gov/drugsatfdadocs/nda/98/20905_arava.cfm#:~:text=Approval%20Date%3A%209%2F10%2F1998

[88] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=060593

[89] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021999s000_toc.cfm#:~:text=Approval%20Date%3A%2012%2F19%2F2006

[90] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=019358

[91] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=062758

[92] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=006525

[93] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=009182

[94] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=050529

[95] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=080036

[96] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=080366

[97] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=084955

[98] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=084148

[99] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=080040

[100] https://cdscoonline.gov.in/CDSCO/Drugs

[102] https://www.google.com/search?q=Cloxacillin+CAS+NO&oq=Cloxacillin+CAS+NO&aqs=chrome..69i57j0i22i30j0i390l4.1227j0j15&sourceid=chrome&ie=UTF-8

[103] https://www.google.com/search?q=Dicloxacillin+CAS+NO&oq=Dicloxacillin+CAS+NO&aqs=chrome..69i57j35i39i362l8.408j0j15&sourceid=chrome&ie=UTF-8

[104] https://cdscoonline.gov.in/CDSCO/Drugs